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THE theme of my address is perhaps unusual. Man the Unknown, might be a suitable title but it savors of plagiarism so I will call it, A Man, Little Known. Him to whom I refer must have had considerable influence upon modern obstetric education and practice. He was a product of the Edinburgh University or of the educational atmosphere of the Edinburgh of the eighteenth century. He left no published books, though some notebooks, apparently those of students, written in longhand are extant—how many there are I do not know, but I have seen three. The name of him to whom I refer is Dr. Thomas Young, first lecturer and full Professor of Midwifery at the University of Edinburgh.

Turner in his history of the University of Edinburgh states that

"It is a noteworthy fact that in the year 1726, when John Rutherford and Andrew St. Clair began assiduously to teach medicine, the Town Council made, in the person of Joseph Gibson, the first appointment of a Professor of Midwifery in Britain. He was succeeded by Robert Smith in 1739, Thomas Young in 1756, Alexander Hamilton in 1780, James Hamilton in 1800, and Sir James Young Simpson in 1840. It is remarkable that the class of Midwifery did not become compulsory for students until 1833, after great exertion and legal action by James Hamilton, the Professor.

"The Maternity Hospital of the present day had its origin in the attic storey of the old Royal Infirmary which, under Professor Thomas Young, early in the eighteenth century, had been devoted by the Managers of this Institution to the treatment of lying-in women. Here practical instruction in obstetrics was given by Young and by Alexander Hamilton who, towards the close of that century, took over Park House, on the site of the present University Union, as a private hospital for this purpose."

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

It is recorded in the notebook of one of his students which I have in my possession that Young stated:

"They began pretty early for to see the advantages of having this branch taught here, about 1725 and in 1726 Mr. Joseph Gibson was appointed to be the city professor and the Town Council enacted: That no woman should be allowed to practice midwifery in or about Edinburgh unless she had undergone an examination by some of the College Physicians and some of the Surgeons with the Professor of Midwifery and Mr. Gibson did intend to give lectures upon midwifery as he published a syllabus containing 22 lectures, but he never taught it as he died soon after, and as the midwives had not an opportunity of being instructed in this branch it was impossible for them to undergo any such examination, so that I have the pleasure of being the first who introduced the teaching of midwifery into this city, and though I met with many difficulties in getting the women to submit to be delivered by men, I have now got these difficulties pretty well over and we have now all the advantages in teaching it here that they have in any other places."

It will be of considerable interest to view the origin of the professorship of midwifery at Edinburgh. Some confusion has apparently arisen relative to this professorship because of difficulty in understanding the exact relationship between the authorities of the city of Edinburgh and the University of Edinburgh itself. Grant, in his story of the University of Edinburgh published in 1884, gives information relative to the establishment of a professorship of midwifery. This occurred on the ninth of February, 1726, when the Town Council added four new professors to the staff of the college and appointed a professor of midwifery. There was a distinction between this professorship and the other four in that the professor of midwifery was not professor at the college but was a City Professor. This was probably due to the fact that the college was for male students of medicine, and obstetrics was almost exclusively in the hands of the midwives. It was, therefore, not deemed necessary to teach medical students the art and science of obstetrics.

It appears that Mr. Joseph Gibson, somewhat ahead of his time, had practiced obstetrics in the town of Leith. Upon the insistence of members of the Colleges of Physicians and of Surgeons and largely upon his own initiative he was created by the Town Council the "Professor of Midwifery in this city and privileges to profess and teach the said art in as large an extent as it is taught in any city or place where this profession is already instituted." It appears, at least from a statement of Thomas Young in his notes, that Gibson did plan to teach obstetrics and prepared a syllabus for this purpose, but he never actually taught midwifery. Gibson died in 1739, and he was succeeded by Mr. Robert Smith who "received the title of Professor of Midwifery in this city's college with the same privileges and immunities which the other professors in said college do enjoy or that are known to appertain to a professor of midwifery in any other well regulated city or place."

Apparently neither Gibson nor Smith taught medical students in this branch. Gibson may have taught the midwives, but according to Young's statement he did no teaching because of his death before the plan was put into operation. It is of interest to note that the Council at Edinburgh seemed to be thoroughly unaware that they were creating a precedent. The first professorship on the continent was at Strasbourg and was founded in 1728. Obstetrics was taught in other places both in

England and on the continent. Literature emanated from men interested in midwifery in various cities and countries, but little, if any, had come from Edinburgh at this early date. It is difficult in this day and age to comprehend the many obstacles which were thrown in the way of so-called men midwives. There was a very great prejudice against men even being present at the time of birth. It, therefore, took a great deal of courage and foresight for the Colleges of Physicians and of Surgeons, for the Town Council, and for Mr. Thomas Gibson to advocate the practice of midwifery by men and to create a professor in the city of Edinburgh who would be responsible not only for the training of the midwives, who were at that time receiving no education in midwifery in that area, but also to envisage the future training of medical students as men midwives. The profession was considered unbecoming for gentlemen and improper or immodest for the women being delivered.

Professor A. R. Simpson has written an extensive article relative to the history of the chair of midwifery at Edinburgh. This lecture was published in 1882.

He says, "It would have been interesting to have known more than we do of Mr. Joseph Gibson, who was probably the prime leader in the whole transaction, and who was certainly the first Professor of Midwifery in the United Kingdom, if he was not indeed the first to fill an obstetric chair in any University." There is a paucity of information relative to this man who is described as "surgeon at Leith, member of the Society of Chirurgeon-Apothecaries in Edinburgh, and city professor of midwifery."

As City Professor Mr. Gibson, having the right to teach, still was not a member of the medical faculty of the University and had no place in the Senatus Academicus. Very little is known of Gibson and his activities. He died in 1739 after serving as City Professor for 13 years.

Mr. Robert Smith succeeded Mr. Gibson and we have the following notes from Dalzel's History of Edinburgh University which he has quoted from the proceedings of the Town Council:

"On February 9, 1726, Mr. Joseph Gibson, upon petition, appointed City Professor of Midwifery, but without fee or salary." Also the entry of Dec. 14, 1739: "Mr. Robert Smith, surgeon, elected Professor of Midwifery in the College, on the death of Joseph Gibson, Professor thereof in the city, but without a salary." (Smith's commission was ampler than that of his predecessor; it constituted him a member of the Senate. He held this Professorship 17 years.)

What he did and what he wrote is a mystery. He was a member of the Senatus and yet was never admitted as a member of the medical faculty. There is no available record of any of his activities or publications. On Feb. 18, 1756, the following note appears in the proceedings of the Town Council: "Mr. Robert Smith's demission of the Professorship of Midwifery in the college of Edinburgh. Thomas Young, surgeon, chosen in his place. No salary." (Young opened a class for students in this branch of medical practice, not confining his attention to the education of females.)

Dr. Thomas Young apparently had been teaching midwifery in Edinburgh since 1750 and was evidently a very energetic individual, but no record of his activities, of his birth, education, etc., is available. His

name appears in the records of the Royal College of Physicians of Edinburgh as having received his Diploma Nov. 3, 1761, at Edinburgh, which was followed by a license to practice Dec. 8, 1761, and of his admission to Fellowship on Nov. 2, 1762.

He published in Rotterdam a thesis under the date of 1769, in Latin, the abbreviated title of which is "De Lacte," in which he is cited as a Briton graduated in Edinburgh Nov. 30, 1761.

Professor Simpson, in his historical article states that, "he had in his possession three manuscript notes of Young's lectures which were sometimes in one and sometimes in two or three volumes." He states that "they bear evidence to his wide acquaintance with the literature of his subject, and his excellent power of observation and exposition."

Professor Hamilton, adjunct and successor of Professor Young, wrote the following statement of him:

"This, among many other happy consequences, has been the effect of the public instruction of midwives, a measure introduced into Scotland by the late Dr. Young. Before this time any woman of intrepidity and address who chose to practice midwifery found employment; and for a while it required all his industry and professional talents to show the folly of trusting the delivery of women to such persons. Even they who pretended to the sacred name of philosophers joined in the prejudice. Dame Nature, they said, is the proper midwife, and nobody can be better qualified to attend to her dictates than Dame Ignorance. Dr. Young might with great facility, by publishing a few of the horrible blunders committed by the midwives resident in Edinburgh when he began practice, recorded in his note book (which is still in existence), have offered many most powerful arguments against such opinions, but he preferred the more philanthropic and dignified method of showing by its effects the utility of his plan. Such has been the public conviction on this subject that in the present day there is scarcely a parish of Scotland the midwife of which has not been regularly taught. If the difficulty of instructing women to act as midwives, and Dr. Young's disinterestedness in that task were universally known, a just tribute might be paid to his memory."

The following are some of the official records which evidence Young's pioneer work in the teaching of midwifery. He apparently established free home delivery service as he made public announcement of the fact that patients would be delivered in their own house free of expense. It is also a matter of record in the history of the Royal Infirmary that "in 1756 a ward in the attic story of the hospital, by the permission of the managers, but at Dr. Young's expense, was fitted up for four lying-in women, or as many more as Dr. Young could accommodate, each exceeding the number four paying sixpence per day to the house."

Dr. Young alone taught his classes for 24 years, and in 1780 he and Dr. Alexander Hamilton were made conjunct professors of midwifery. This arrangement enabled Dr. Young and Dr. Hamilton to give courses of instruction alternately, three in number, each year to male and female pupils. On the death of Dr. Young, Dr. Hamilton continued as the sole professor of midwifery, in 1783.

Largely through the efforts of Professor Hamilton and the activities of the Earl of Levan and Melville, the Edinburgh Lying-in Hospital was established in 1791. Certain rules of the Royal College of Physicians at Edinburgh promulgated at this time are of interest in this connection and show the attitude toward midwifery and the shifting opinions which occurred in the space of a generation.

"17th May 1765.—An act was passed declaring that for the future no person should be admitted to be one of the Fellows, 'whose common business it is either to practise Surgery in general, or Midwifery, Lithotomy, Inoculation, or any other branch of it in particular; and further, that if any member of the College shall, after his being received a Fellow, practise any of these lower acts in the manner above mentioned, and shall thereof be lawfully convicted, he shall be degraded from the honour conferred upon him when he was admitted a Fellow, and his name shall be struck out of the Roll.'

"7th February 1769.—After full consideration by a Committee, and repeated discussion in the College, an Act was passed providing that no Fellow or Licentiate of the College should exercise the business or profession of Midwifery, Lithotomy, or any of the other manual operations of Surgery; and providing that, if lawfully convicted, he should be fined 40 pounds Scots for the first offence, and for the second, if convicted, he should forfeit his right of Fellowship, if a Fellow of the College, or his right of Licence, if a Licentiate, and all right and title whatever to practise physic within the city of Edinburgh and liberties thereof.

"7th November 1769.—The Act of 7th February was rescinded.

"6th August 1772.—The Act of 17th May 1765 was amended on the Report of a Committee to whom it had been remitted for consideration."

I have had little opportunity to peruse the manuscript notes of Young's lectures which are in the Library of the Surgeon General at Washington. However, one of them is an exceptionally beautiful example of manuscript notes. The title page bears the name of John Whyte and is dated the 14th of November 1771. This John Whyte subsequently became Whyte-Melville through marriage and is undoubtedly the Earl referred to as being influential in establishing the Edinburgh Lying-in Hospital. This manuscript is beautifully executed. The title page bears a quotation, Genesis, Chapter 3, Verse 16, "In sorrow shalt thou bring forth children." The first paragraph on page one is similar to the initial statement in the manuscript copy which I possess. I quote from the manuscript copy of John Whyte: "The word midwifery is taken in two different senses, the one is limited and confined and the other more extensive. The first takes in only the delivering of pregnant women, the second not only includes the operation but also all the diseases incident to unimpregnated women as well as those in pregnancy and after delivery."

The other notebook in the Surgeon General's Library is undated, but is beautifully written and prepared. The first page reads as follows:

"As Midwifery is a modern operation, consequently its history is shorter than that of the other Branches of Physic. I shall now go on to mention some of the measures that have retarded that Branch and then the several steps that have been taken to cultivate it. Long and sad experience have taught us in the clearest manner that this is one of the most useful, if not the usefullest operation in Surgery. For by it you often save two lives as in praeternatural cases and violent floodings when danger to one or both is very often unavoidable. Whereas by the help of a skillful operator we will often be able to save both from their impending danger. It lay a long time uncultivated from its being entirely in the hands of women and these the most illiterate, having no education and no skill of the anatomy of the parts. In fine all the learning they had was from Experience: hence we need not wonder at the blundering on from century to century. The Athenians were so sensible of this that they made a law against any woman practising Midwifery. In consequence of which a woman dressed herself in men's clothes, went away and was educated, came home again and practised midwifery and got into all the women's secrets. However she was detected and forbid to practise any more."

He clearly states that Smellie was the first who made any considerable improvement in teaching midwifery.

It is curious that while Gibson is mentioned, the name of Smith does not appear in the manuscript which I possess. It is interesting to note that Young records an interesting item that "Chapman was the first to discover the secret of forceps and reported six cases which he delivered with them." He makes this comment relative to Mr. Chapman: "Whereas before that time they (forceps) were only known to the Chamberlains so that the material contained in these books (Chapman's) is the discovery of the forceps. He likewise pretended to a secret pellet (for it was the fashion of the time that every practitioner be possessed of some nostrum either of the pellet or of some quickening pill or powder which assisted the labour more quickly) but his secret pellet died with him."

Young devoted considerable discussion to the theories or system of generation. He makes the following comment: "But it is evident that we are still much in the dark in regard to this matter. After all the theories that have been started we can't see why there is not a regular communication between the ovaria and the fallopian tube. It seems, however to take place at some time. Nor is it easy to explain how the male liquor enters the uterus and so in short every system that has been offered upon this subject is liable to the greatest objection, and we will not be able to understand it thoroughly."

He discusses ectopic pregnancies and states that they seldom come to any degree of perfection, seldom larger than three or four months and that they are more common in the ovary than in the tube.

He devotes considerable discussion to the toxemias of pregnancy, recognizing those cases associated with marked edema or dropsy and also the cases associated with fits or convulsions. These latter he divides into two main groups, those women who gave a history of having had fits, probably epileptic seizures, and those without such an antecedent history. The latter he regards as much more serious.

A few of his comments relative to these cases may be of interest. With reference to the fits he says:

"These will happen to women with child that never had the disease before; and they happen more frequently in a woman's first child than afterwards perhaps owing to this that the irritation is greater from the nerves being more sensible than they are ever afterwards. If the woman has been subject to these fits before there is less danger to be apprehended from them. These are also more or less dangerous in proportion to the frequency and when they are very frequent the woman frequently dies."

He reports a case upon which an autopsy was performed and no cause of death could be determined. The etiology is explained in the following paragraph:

"The fits may be owing to a great many different causes. The common cause is from the uterus pressing upon the iliac arteries. When this pressure is very strong it affects the aorta and by preventing the same quantity of blood from going to the under parts it occasions an overdistention of the vessels of the brain, and the woman being at this time in a plethoric state the circulation is rendered more languid which may favour the production of these fits."

He says: "There occurs also an irritable system peculiar to pregnant women." The outlook for the women who have these fits during labor is better than those who have them during pregnancy. He makes an interesting observation that the outlook is better for those who have had the fits before and also for the women who come out of them and recover their senses more quickly. He recognizes that the usual remedies for fits are of little or no service to pregnant women. He advocates venesection and prompt delivery as the best means of treatment.

It is curious that he gives the period of gestation as 270 to 275 days or 39 weeks. He also discusses premature births and makes a very interesting comment to the effect that "the child is often born in the seventh month and children were more commonly supposed to live then than when they were born in the eighth month because they thought the child made an effort to be delivered at the seventh month and if it did not come away then it required 40 days to recover strength, therefore if it happened to be delivered in the eighth month and being still fatigued it died, but this notion is not just, for the older the fetus the greater is the probability of its living."

Relative to the labor itself he says: "You need make no change in your dress for natural labour. Formerly as soon as a man midwife entered the room he put off his waist and put on his nightcap, put off his coat and put on a nightgown and put up his sleeves to his shoulders, but all this must cause a great terror to the woman, and in natural labour it is not necessary to make any change upon your dress. It is easy to slip up the sleeves of your coat and to take out the button of your shirt and put it up a little to keep it clean, and as you are generally situated behind the curtain you may do it unobserved, and those who wear a ring should take it off as it would injure the woman when the hand is introduced into the vagina."

He divides births into natural birth, laborious birth, and praeternatural births. He taught that "many things have been recommended in order to further the births but in many cases patience will do much more than any medicine. These at times have been thought successful because the delivering of a woman is a natural operation, so if your medicine is well timed it seems to do good and at other times it is rather too late and the woman is delivered before it arrives."

He thought forceps could be used for delivering women with the following positions of the head: "when the hind head is toward the os pubis, toward the os sacrum, when the face is toward one os ischium and the occiput toward the other."

He advocated the reduction of the following positions before the application of forceps: "when the chin is toward the os pubis, when it is toward one side of the pelvis, and when it is toward the os sacrum."

His indications for cesarean section are as follows: "It is performed when the mother is dead to save the child and also when the mother is alive in order to save both her and child, when from the extreme narrowness of the pelvis it is impossible to extract the child the other way. No one ever disputed the propriety of the operation in the former case; nay, in some cases it was considered as a capital crime to prevent the opening of the woman when dead in order to procure the child. In the latter it has not been so universally submitted to, and it is evidently as necessary here as in the other as without it a mother and child must both infallibly perish. While by means of it there is a possibility at least of saving the mother and a certainty almost of preserving the child."

He gives the following description of the operation:

"Before the operation it is proper to give the patient a quick dose of physic or an injection in order to empty the bowels. This done you either place her on a table or bed in such a manner that she may be half lying and half sitting as when one is cut for the bubonocele. The operation is generally performed upon the left side in order to shun the liver, but it is not material whether you do it on the right side or left side as the uterus rises above the liver and sometimes the uterus inclines more to one side than to the other, in which case the side to which it is most inclined should be preferred. You make a mark on the skin as far as you intend cutting, the length requisite is about 8 inches and the incision is generally made half way between the navel and spine of the ilium, but it is not very material, and it is

more important that you do not carry the incision too high or too low as the bowels are in danger of coming out, therefore the best place to begin is just a little above the navel and it is of advantage never to go too high. Some pinch up the skin in order to make the incision, lest they should open any considerable branch in an artery in which case the blood is in danger of getting into the cavity of the abdomen. However, it is very easy matter to take them up. You cut cautiously till you once get admittance for your finger which you are then to use for a director for your scalpel. Having got into the cavity of the abdomen you know the uterus from the other parts from its firmness and its being of a different color, then as before you first make a small incision for your finger and using it as a directory for fear of injuring the child you proceed to lay open the uterus, but were you to go on gradually cutting here as in the other parts the large uterine vessels would not be allowed to contract but would continue to pour out their blood. You therefore cut the rest quickly and get out the child as soon as possible whereby the incision is diminished the one half and the size of the vessels are proportionately lessened. If the child's head is much locked in the pelvis you will find a difficulty in getting it out. In this case you cause some one to introduce a hand into the vagina and push up the head while you pull the body. Also in consequence of this sudden contraction of the uterus the placenta is readily disengaged and you get it away with great ease. You next clear away all the extravasated blood that is upon the intestines, etc., and you bring the lips of the wounded uterus as close together as you can after waiting a little until the blood is pretty much stopped. You next bring the external parts of the wound together by the quill suture. You need not make the ligature so close below as the bowels are chiefly in danger of coming out at the upper side, and a small opening at the lower part of the wound serves for the passage of any moisture that may be generated. It is not necessary to take up the peritoneum and you tie the ligatures with a loop in case you find it necessary to untie again. The most disagreeable and hardest to be remedied accident that attends this operation is the forcing out of the intestines, as the handling them in order to reduce them often excites coughing, vomiting, etc., with protrusion anew."

He had performed the operation twice at the time of the unknown date of my manuscript copy, with the loss of two mothers and one baby.

He understood the mechanics of labor well and gives a clear description of the indications for operative and delivery technique. He discusses the management of the third stage and gives the following lucid instructions:

"The uterus is so formed that the moment it is freed of its contents it only contracts by degrees so that everything which is in it comes to be expelled but to forward this extraction you twist the umbilical cord around your hand and pull from side to side making the woman press down a little, and when it comes to the external os you move it in a circular direction. The proper time to begin is when the woman has afterpains which are proof that the uterus is beginning to contract. You are not, however, to expect that you will always succeed immediately. It may be ten to fifteen minutes and even an hour sometimes before you get it away, but you will generally succeed at last and with perfect ease to the woman."

He appears to have been greatly interested in the phenomenon of respiration and discusses the necessity of breathing air for both oviparous and viviparous animals. He quotes Harvey's opinion to the effect that the fetus may live some hours wrapped in its membranes without breathing. He quotes an experiment by Buffon "who confined a pregnant bitch so that she was under the necessity of dropping her young into a quantity of warm water which he placed to receive them; the animals remained several hours in this fluid and were quite lively and well."

He describes methods of resuscitation and emphasizes the necessity of removing anything from the face or mouth which might interfere with respiration and suggests the use of a female catheter to force air into the lungs and stimulate respiration.

He evidently carried on some experiments of his own and calls attention to the effect of closure of pores in the eggshell on the accumulation of air within the egg and the effect upon the development of the chick.

He advocates milk as the proper food of all viviparous animals and contends that no milk is so well adepted for children as mothers' milk. He argues against the use of purgatives for newborn infants in spite of the fact that he recognizes a general prejudice in their favor.

He has a paragraph or two relative to puerperal fever, and he did thoroughly cleanse the ward and take measures to remove the "pestilence" as he termed it and subsequently had only one case which died in the ward where he had removed the bedding and substituted fresh bedding and thoroughly washed the room with soap and water.

The following is a quotation which concludes his discussion of puerperal fever:

"In this way then we have found no particular cure for puerperal fever but cleanliness is perhaps the best thing in order to prevent it from taking place. Purgatives, emetics, camphor bark and all the different antiseptic medicines have all failed in removing this here disorder."

He gives some pertinent advice relative to the selection of a nurse: "You should choose a woman who has all the appearance of health, who has no disease either hereditary or acquired, as this is a matter of consequence. Care must be taken to examine her children to see whether they have any appearance of any disorder as the scrofula does not appear on children generally speaking before the third or fourth year; for satisfaction in this matter you may examine her parents or brothers and sisters."

He closes his series of lectures with some advice to his students:

"Before we part I shall give you some few directions with regard to your conduct. Some of you are going immediately to enter upon practice. I told you it was unnecessary to read any books in the first course, but now you must consult some of the best authors upon this subject as you will now be able to read them with pleasure and benefit. You should therefore consult the writings of LaMotte, Mauriceau and Smellie; and you can't have a better compendium than in the writings of van Swieten, who has wrote very fully upon the diseases of both Women and Children, as you must be as much master of cases as possible in order to be able to give a certain prognostic by which you will at least gain reputation, when you cannot cure; so you must not only take the assistance of these cases you read, but of those which happen to yourself; and I can assure you the one who writes down his cases will have more experience at the end of 5 years than another who does not will have at the 10 hundredth. You should therefore write down in a day book what has happened during the day, where you succeeded and where you failed; particularly in the laborious cases which will plague most, and you must mention the progress of the dilatation of the mouth of the womb and the whole progress in short of the labour.

"It is common to mention the necessary qualifications for a man midwife. They are pretty much the same with those of a good operator, only a greater degree of composure is here necessary; for a small oversight is of the greatest consequence; and in other operations you have the assistance of your eyes, but here you have no such assistance. A becoming share of modesty is especially necessary here. You should not put any question to your patient which will shock her, and you had better put them to another as to her maid, her nurse, etc., especially if they are such as can be fully answered by a third person. When you are called to assist women in natural labours you should not be in too great a hurry in putting them to the touch; it will be proper to put them to bed, to darken the room to a certain degree, and to have as few assistants as you can, and you should make as little alteration in your dress as possible. Everybody knows what should be done in a common labour so your conduct will be strictly observed and the smallest blunder will be severely censured. In a praeternatural one they do not know so well what is necessary so

that you may use more freedom. After the delivery you should make yourselves tolerably decent before you go out of the room in order to give some time to the nurse to shift the patient; and when you have allowed time for this you may return to give your prescriptions. A degree of secrecy is very necessary. Therefore you should beware of relating the oddities of one patient to another, for if you do she will naturally think that you will do the same to another with regard to her. If your patient has a peculiar distemper and you can relate to her perhaps a similar case, it may be of service, but you must never act wantonly in these cases; and you must be still more cautious in revealing to any of her own sex what you learn; and therefore in every case you must act and speak with the utmost decency and decorum, and never betray the confidence reposed in you by harbouring any bad or indecent design. They are little acquainted with the greater and better part of the sex who expect that women will forgive such faults. Errors in judgement they may forgive, but such behavior they never will, whereas if you behave in a becoming manner there is no fear but success will attend you, which that it may is the sincere desire, of your most humble servant—Thomas Young.''

In concluding this necessarily brief record of Professor Young it should not escape our notice that men who subsequently became very influential in our own country received their education and were granted their degrees during the years when Professor Young was Professor of Midwifery in the University of Edinburgh. He was one of a galaxy of brilliant men associated with the university of that period. His fame is less than theirs, but nevertheless he must be credited with founding modern concepts and methods of teaching midwifery. It is important to emphasize that Edinburgh through its Town Council and university unwittingly and without ostentation created the first professorship and university department of midwifery (1726-1756), which is recorded in the world literature.

These concepts and methods were brought back to our country by such men as William Shippen of Philadelphia, Samuel Bard and John Tennent of New York. It is impossible to calculate the influence of a man who has left so little written record of himself or his works, and we can only surmise that he must have had a very potent influence in the community and in the world at large. I have already mentioned the manuscript in the Surgeon General's office bearing the signature of John Whyte who later became Whyte-Melville and undoubtedly became interested through his contact with Young in establishing the Lying-in Hospital at Edinburgh.

William Drennan, a famous Irish patriot and writer, studied medicine in Edinburgh and graduated in 1778. This Irish patriot, writer, and poet subsequently practiced medicine in Ireland. In some records written while he was a student in Edinburgh he refers to the first course in midwifery by T. Young and says that ''after dinner I have seldom more than 1 hours attendance at the college and that is on midwifery.'' He entered the University in 1773 and sat for his examination in 1778.

It was through an accident a number of years ago that I acquired this manuscript copy of Young's lectures in Edinburgh. It is undated, but probably was written in the latter part of 1771 or during 1772. It could not have been prior to 1770 or 1771 as he gives references to these dates in the manuscript.

It has been with a great deal of pleasure that I have endeavored to unearth and clarify some of the facts with reference to his life and his

influence. He apparently worked thoughtfully, seriously, and energetically with enthusiasm over a period of at least 33 years, and he was the first full Professor of Midwifery, the first teacher of medical students in midwifery at the University of Edinburgh which post he filled for 27 years. Men well known receive adequate praise and credit as well as criticism at times for their accomplishments. The man little known doubtless received much satisfaction from his work and made no effort to secure the acclaim of others. Thomas Young undoubtedly deserves great credit and unsought praise for establishing a great work in obstetric practice and education. He founded in Edinburgh University the modern concept of the teaching of obstetrics, and his influence has continued there and has spread through his students who became pioneers in obstetric teaching in our country. We should acknowledge our debt to him by belated but sincere praise.

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HORMONAL STUDIES IN ARTIFICIAL MENOPAUSE PRODUCED BY ROENTGEN RAYS

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INTRODUCTION

SINCE 1930 it has been the routine in some of the cancer clinics of this community to inactivate ovarian function by means of the roentgen ray in patients who have carcinoma of the breast before the menopause. The rationale of this therapy is to avoid possible stimulation of malignant breast epithelium by the ovarian hormones.[1] Regression of osseous metastases has been noted following such treatment.[2] A group of patients so irradiated offer an excellent opportunity to study the hormonal changes attendant upon this type of menopause, especially since the patients had no demonstrable disease of the genital organs.

In this investigation studies of urinary excretion of the follicle-stimulating hormone (gonadotropic hormone, prolan A) and estrogenic substances were made at frequent intervals on the urine of 10 patients who were thus irradiated following radical mastectomy. Two other patients, one a surgical castrate and a second sterilized by radium, are included in the series for comparison. Random observations were made on 10 other patients who had been sterilized prior to this study. In most instances, assays of the urine for follicle-stimulating hormone and estrogens were made for a short period preceding irradiation of the ovaries and thereafter at regular intervals during periods varying from one and one-half to three years. The patients were examined and questioned carefully at each visit so that the first signs and symptoms relative to the menopause could be correlated with the laboratory findings. Symptoms of the menopause were considered to be cessation of menstruation with accompanying hot flushes, night sweats, dizziness, increased nervous tension, and atrophic changes in the vagina.

TECHNIQUE OF OVARIAN IRRADIATION

The following factors were used to effect ovarian sterilization: 200 K.V., ½ mm. cu. filtration, distance, 50 cm. or 77.5 cm. Total dosage varied from 1,200 to 1,600 r. divided over a period of four days and given through anterior and posterior portals. The portals were 10 cm. by 10 cm. or 15 cm. by 15 cm. Various combinations of the above factors, maintaining a constant voltage and filtration, were used to determine if possible the most efficacious means of obtaining the desired result.*

METHODS OF HORMONE ASSAY

The original technique of Aschheim and Zondek for determination of the urinary follicle-stimulating hormone was employed. This consisted of an alcoholic precipi-

*We are indebted to Dr. Richard Dresser for carrying out the above procedures.

tation of the urine with subsequent assay of the hormone on immature inbred black mice (Bar Harbor strain C57). Except in several instances no attempt was made to assay for follicle-stimulating hormone in titers of less than 80 M.U. per twenty-four-hour specimen. Methods published since the onset of this investigation are probably more accurate for the quantitative assay of follicle-stimulating hormone, but as far as we are aware none of the techniques available are capable of furnishing more than a relative index of the total hormone excretion of the gonadotropic hormones. This method has been found suitable for our purposes, since we were interested only in gross differences and did not consider values below 80 M.U. especially significant.

The technique of Smith and Smith[3] was employed for extraction of the total urinary estrogens. This consisted of acid hydrolysis of the urine and subsequent extraction with benzol. Assay was then performed on spayed female adult black inbred mice (C57) according to a minor modification of the Allen-Doisy technique. This method is capable of detecting minute quantities of the hormone. The assays for both follicle-stimulating hormone and estrogen were carried out on complete twenty-four-hour specimens of urine, so that all figures presented represent the total daily output.

RESULTS

The charts shown were selected from the entire group of patients to present graphically the essential observations in this study. Of the points illustrated in these, the following are worthy of mention:

Following irradiation of the ovaries, although fluctuations did occur, there was a gradual diminution in the excretion of the urinary estrogens until a fairly constant level considerably below normal was reached. As the estrogen excretion decreased, follicle-stimulating hormone appeared in the urine at levels of 80 M.U. or higher per twenty-four-hour specimen (M.P., Fig. 1, M.S., Fig. 3, E.K., Fig. 5). In general, however, this titer was obtained only when the estrogen levels were exceedingly low. Occasionally it increased before that time, while the estrogen was still elevated, though below the normal level (F.R.) (Fig. 2).

Menopausal symptoms commenced within one to seven weeks after the detection of follicle-stimulating hormone, but most often within two to three weeks. It should be emphasized that the symptoms did not occur in the presence of low estrogen levels alone, but only when there was a relatively high titer of follicle-stimulating hormone. The above chain of events occurred more rapidly in the oophorectomized patient (A.W., Fig. 4) and less rapidly in the patient treated with radium (C.M., Fig. 4).

In three instances (F.R., Fig. 2, M.M., Fig. 3, and A.B., Fig 2), the first attempt to produce permanent amenorrhea with roentgen treatment was unsuccessful although a temporary cessation of the menses occurred. Two of these patients (F.R. and A.B., Fig. 2) received another course of treatment which was followed by permanent amenorrhea and the symptoms of the menopause with the corresponding changes in the hormonal excretion. In the third patient (M.M., Fig. 3) who was near the climacteric, further treatment was refused. Later this patient had a permanent cessation of menstruation resembling that of a spontaneous menopause following several normal periods. Before the recurrence of her menses, there was a marked rise in the estrogen excretion and a decrease in follicle-stimulating hormone to levels below 80 M.U. per twenty-four-hour specimen, with a cessation of hot flushes. It was possible in these cases to predict a resumption of menses with a certain degree of accuracy because the hormonal titers were known.

The effectiveness of the roentgen ray treatment in producing castration as regards the age of the patient was also studied. Of 6 patients close to 40 years of age only 1 had a period after the treatment, whereas

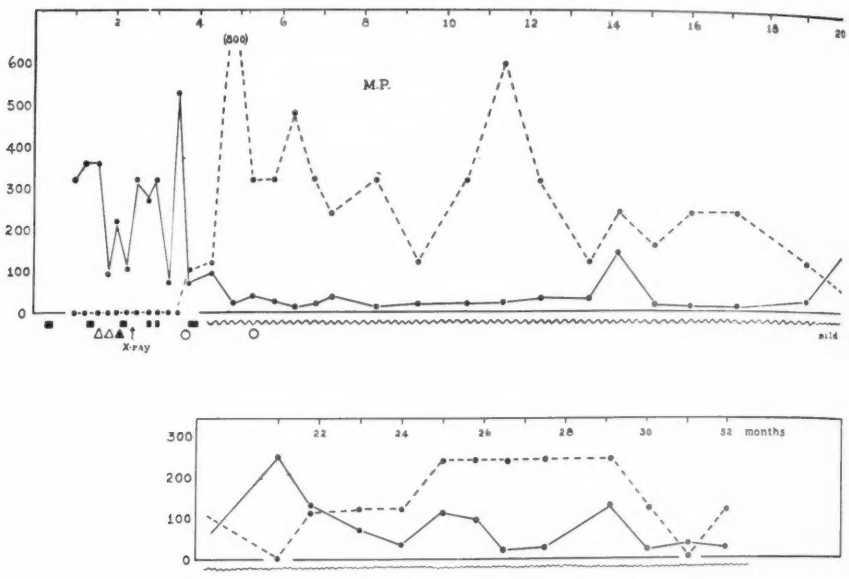

Chart 1.

Charts 1 to 5.—*Broken line:* Follicle-stimulating hormone in mouse units per twenty-four-hour specimen of urine. *Continuous line:* Total estrogens in international units equivalent to crystalline estrone. *Wavy line:* Hot flushes. *Solid block:* Menstrual period. *Open triangle:* Endometrial biopsy, proliferative phase. *Solid triangle:* Endometrial biopsy, secretory phase. *Circle:* Endometrial biopsy, secretory phase. *Ra:* Intrauterine radium. *H:* Hysterectomy and oophorectomy.

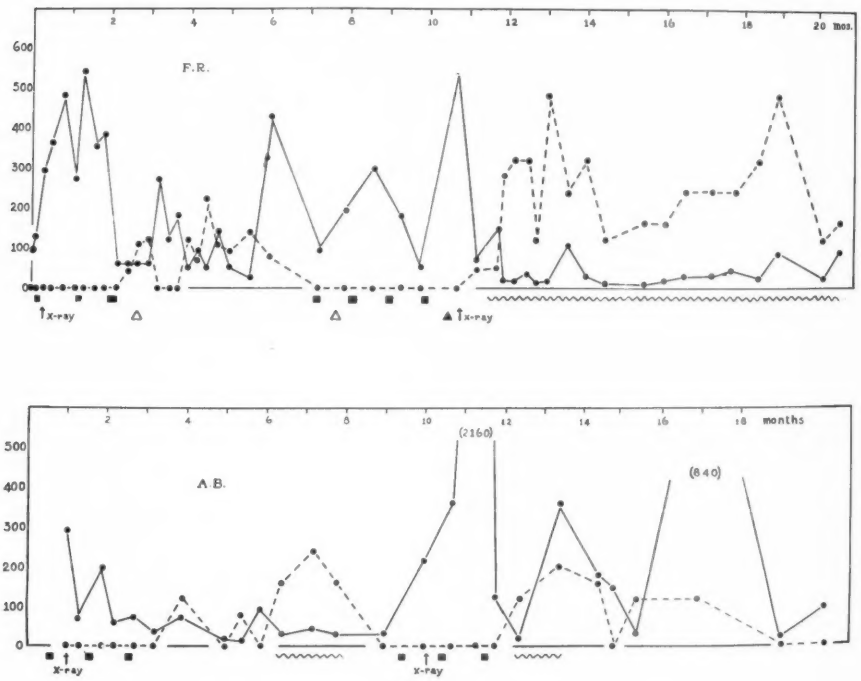

Chart 2.

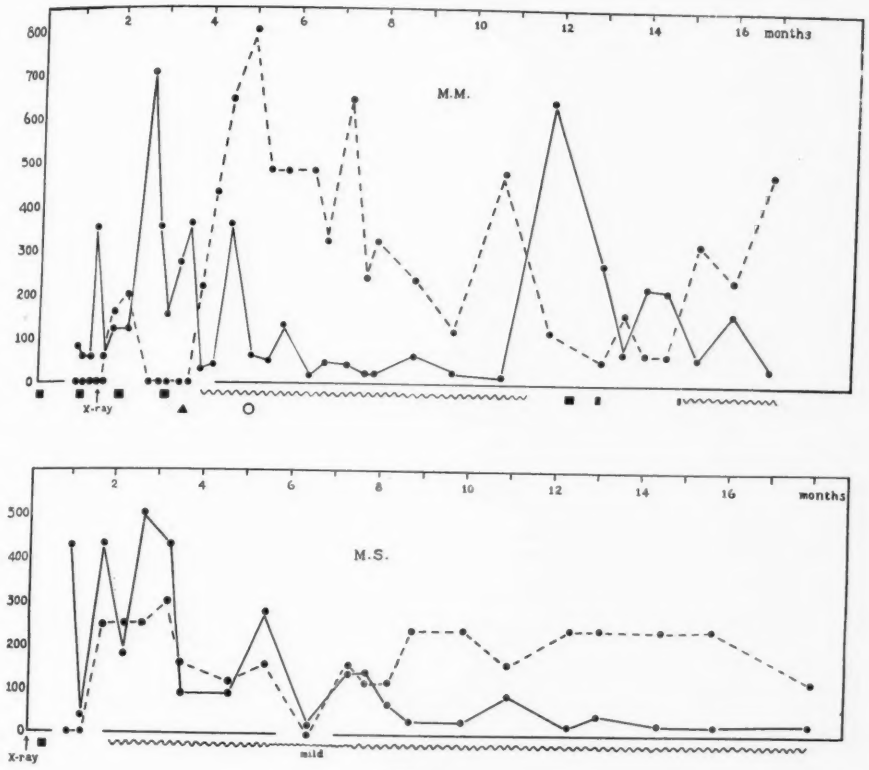

Chart 3.

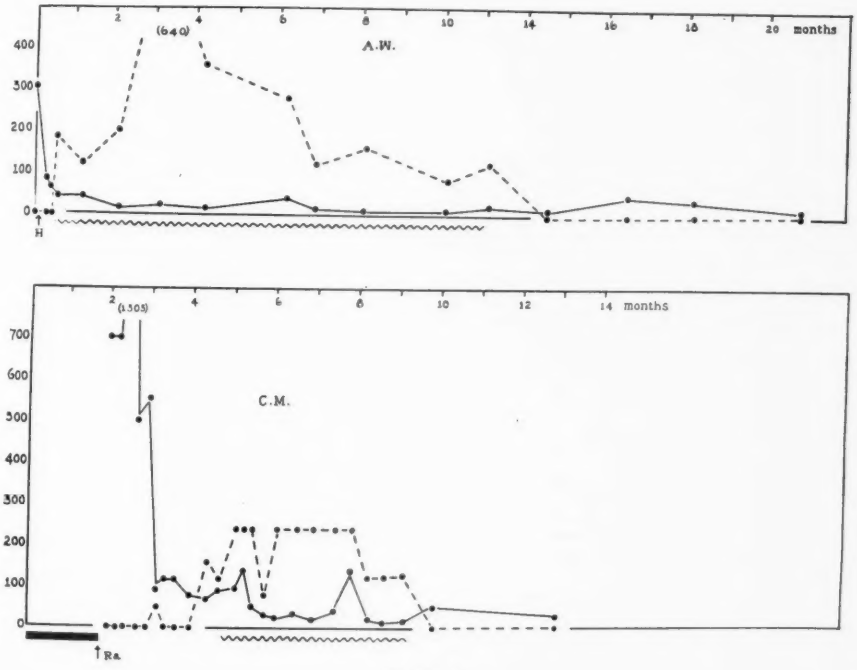

Chart 4.

of 6 patients close to 30 years of age, 5 had one or more periods. The time at which the therapy was instituted during the menstrual cycle bore no relation to the number of periods that followed or to the effectiveness of the therapy.

Endometrial biopsies taken before and after roentgen therapy yielded the expected findings until amenorrhea became permanent. Later attempts to obtain tissue were unsuccessful. In one instance an endometrial biopsy taken just before the expected menses showed a normal

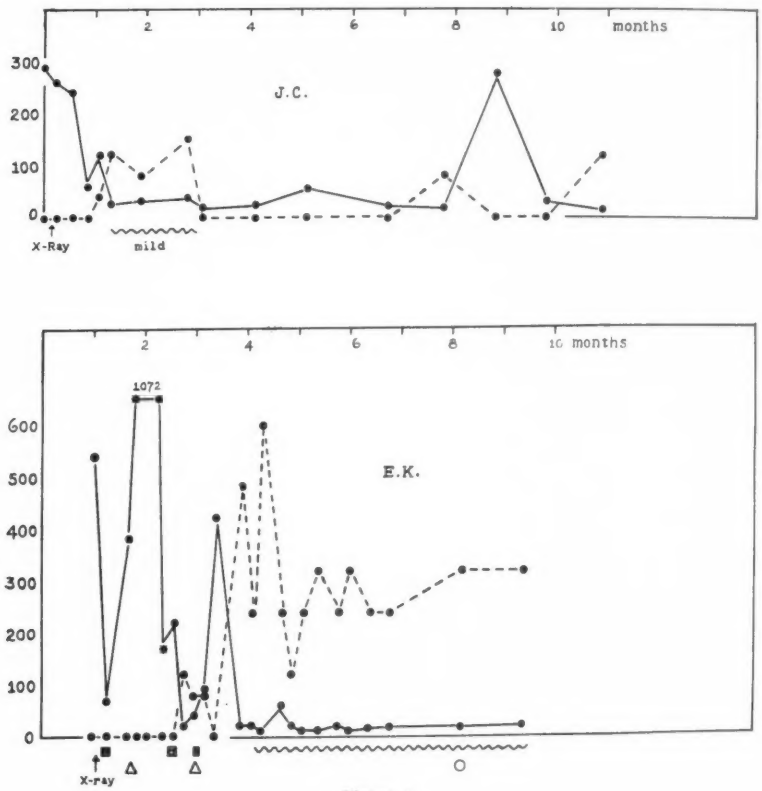

Chart 5.

secretory or functional endometrium and yet the period never materialized, indicating that cessation of menstruation can occur at any time in the cycle. The vaginal mucosa of these irradiated patients resembled those of women in the spontaneous menopause.

Observations on other roentgen castrates (10) one to three years after therapy, yielded findings similar to those shown in the charts. The urine of women assayed during the course of the spontaneous menopause and after its completion usually showed estrogen determinations well below normal. However, follicle-stimulating hormone was not recovered in elevated titers in every patient. The estrogen levels in several of these patients who had an excess of follicle-stimulating hormone, without vasomotor symptoms, were higher than those usually ob-

tained in the menopause. It is also interesting that estrogens were recovered from urine of every patient studied, including the surgical castrates even though the symptoms pointed to cessation of ovarian activity.

DISCUSSION

These studies suggest certain possibilities which necessitate discussion and analysis. Following ovarian irradiation there is a gradual diminution in the urinary estrogen excretion. This is probably due to a direct action upon the follicles as a result of which their activity is suppressed. As follicle secretion decreases following x-ray therapy, the anterior pituitary becomes hyperactive which is manifested by an increased urinary excretion of follicle-stimulating hormone. (Follicle-stimulating hormone in excess in the menopause and after castration was reported by Zondek,[4] and since that time many workers have made the same observation.) Shortly after this the vasomotor symptoms of the menopause appear, but these symptoms are not an accompaniment of low estrogen levels alone, for they seem to be present in most instances only when follicle-stimulating hormone is found in titers over 80 M.U. per twenty-four-hour specimen. This suggests that a certain degree of hyperactivity of the anterior pituitary must exist before symptoms appear. The appearance of these vasomotor symptoms only after the first significant rise in follicle-stimulating hormone, as shown by Albright[7] and by these studies, suggests that hyperactivity of the anterior pituitary is a necessary accompaniment of the symptoms if not the exciting cause. It must be stressed, however, that some factor in the pituitary other than follicle-stimulating hormone may be responsible for the symptoms, for in our opinion the increase in follicle-stimulating hormone merely indicates an hyperactivity of the anterior pituitary gland. It is probable that this may also be shown by assay of other tropic factors. Heller and Heller[5] in a recent study could find no relationship between the gonadotropic potency of the urine and the presence or absence of menopausal symptoms in various types of patients. Our studies on women with a spontaneous menopause partially confirm these results. Although we frequently found elevations of follicle-stimulating hormone in the absence of symptoms, these levels were usually below those detected when vasomotor reactions were apparent. In the presence of symptoms, however, we seldom failed to recover follicle-stimulating hormone in fairly high titers.

In contradistinction to the patients with spontaneous menopause, the laboratory findings in the group reported in this study seem to be fairly well correlated with the clinical symptoms. We made no attempt to assay for quantities of follicle-stimulating hormone less than 80 M.U. per twenty-four-hour specimen since we considered only gross variations as significant. It is possible that the method employed is less sensitive than that utilized by Heller and Heller. The precipitation method in both studies is identical. It differs only in the technique of assay and in the attempt to detect minimal amounts of the hormone. Since they did not carry out assays of the urine for the estrogen, we cannot com-

pare these data. It is possible that the estrogen levels may account for the presence or absence of symptoms even though follicle-stimulating hormone may be present in sufficient quantities to evoke a response with our method (F.R. and A.B., Fig. 2). This may explain the difference in our findings. Our results indicate that symptoms were seldom present when the urine of the patients castrated by x-ray titrated less than 80 M.U. and that they were almost always manifested when the titers were above this level. It seems especially significant that no symptoms referable to the menopause could be detected before the first significant rise of follicle-stimulating hormone, and this suggests that the severity of the symptoms paralleled the levels. A recent study of Fluhmann and Murphy is in accord with this view of follicle-stimulating hormone.[18] One of the cases in this series (J.S.) offers some evidence on this point. It can be seen that the follicle-stimulating hormone in the titer mentioned was recorded on a few occasions and only at this time did this patient have menopausal symptoms. Hot flushes were absent during the rest of the period of study although the estrogen levels were low and the patient amenorrheic. In this particular instance the pituitary gland apparently did not become very hyperactive as a result of castration, and this may explain the absence of vasomotor symptoms. Lassen and Brandstrup[6] could not demonstrate the presence of gonadotropic hormone in all of their patients who were castrated by x-ray or operation. However, they did not assay for less than 400 M.U. per liter, so it is likely that the hormones were present in lesser amounts. The thesis of hyperactivity of the anterior pituitary as a direct cause or a necessary accompaniment of the menopausal syndrome is further substantiated by a study of the follicle-stimulating hormone levels (A.W. and C.M., Fig. 4) over a prolonged period after the symptoms had commenced. The follicle-stimulating hormone, although relatively high at first, gradually decreased, and later could seldom be demonstrated in the urine in titers of 80 M.U. or more. Accompanying the decrease there was a gradual diminution in symptoms which eventually ceased, thus coinciding with this decrease of follicle-stimulating hormone in the urine. This suggests that the gonadotropic function of the anterior pituitary in some patients fails gradually after its original hyperactivity. This is contrary to the findings of Heller and Heller who continued to find large amounts of gonadotropic hormone in the urine of all patients studied long after the symptoms had disappeared. The time required for the metamorphosis varies considerably in the individual patient, but the observations recorded suggest that the more abruptly the hyperactivity occurs the more rapidly it will cease. The symptoms are usually more severe in the group who have had an artificial menopause, but by the same token run a more rapid course and finally disappear. Analogous variations are manifested in the spontaneous menopause. The above findings conform to those of Albright[7] and support his contention that the important change in the menopause may be a hyperactivity of the anterior pituitary subsequent to ovarian failure.

This study further demonstrates the pituitary-ovarian relationship. It indicates that normally a balance exists between the hormones of these glands, an alteration in which may give rise to various symptoms and findings which do not occur under normal conditions. In the presence of normal or large amounts of estrogen in the urine, follicle-stimulating hormone was seldom recovered in quantities of over 80 M.U. per twenty-four-hour specimen. Conversely in our experience a low estrogen and elevated follicle-stimulating hormone was usually found in patients with a spontaneous or artificial menopause. We cannot explain therefore the apparent paradoxical presence and relative elevation of both estrogen and follicle-stimulating hormone levels which were found on several occasions. This phenomenon has also been described by Albright[7] and by Englehart and Tscherne.[8]

The behavior of the patients who resumed menstruation in spite of roentgen treatment of the ovaries seems worthy of comment. In these women the size of the x-ray portal was 10 by 10, distance 50 cm., and the total dosage delivered was 1,200 r. given in four divided dosages anteriorly and posteriorly, through one field in each region. In the others, the portal was 15 by 15 and the dosage varied from 1,200 to 1,600 r. With the latter dosage the skin target distance was 77.5 cm. It is probable that in the three unsuccessful instances the dosage was not sufficient nor the portals large enough to permanently destroy or damage all the follicles. This is clearly illustrated in the case of F.R. where the estrogen excretion fluctuated considerably but never reached a constant level until a second course of treatment was given after menses had returned. In these cases in which the treatment was apparently inadequate the cessation of hot flushes, the rise in the urinary estrogens, and the decrease in follicle-stimulating hormone anticipated the reappearance of the menses. When menstruation did recur a normal rhythm was resumed and the first catamenia after the period of amenorrhea came at the time it would have been expected. This finding suggests that a pituitary rhythm exists even in the absence of menstruation. Smith and Smith[9] have suggested that this rhythm continues throughout pregnancy and one of us (I.T.N.[10]) in an experimental study of inhibition of the estrous cycle in the rodent has noted a similar phenomenon. In some of our patients who had a permanent amenorrhea, there were fluctuations in the follicle-stimulating hormone and estrogen levels throughout the period of study. There were drops in follicle-stimulating hormone and rises in the estrogens, but at no time did the levels constantly approach those of women who menstruate. Watson and others[11] suggest that at the menopause the ovaries gradually become refractory to stimulation by the gonadotropic hormones. The degree of response to stimulation must vary considerably. It is reasonable to assume that in these instances there is incomplete destruction of the follicles so that, although fluctuations do occur, the normal menstrual rhythm is not re-established because of the inability of the ovary to respond sufficiently to the pituitary stimulus. This concept is in accord with the experimental findings of Genther[12] in her study on guinea pigs. She demon-

strated that with insufficient irradiation many of the primordial follicles were not destroyed, continued to mature and were active, since the estrous cycle was maintained. It also seems apparent that the estrogens must reach a certain threshold before the elevated follicle-stimulating hormone levels become lowered and the vasomotor symptoms are alleviated or cease entirely. This is shown in the graphs of those patients who resumed menstruation after a period of amenorrhea induced by x-ray. One may conclude from these observations that resumption of the menses depends upon the activity of the ovary and its ability to respond sufficiently to a stimulus, since a high level of estrogen was found to be necessary before menstruation recurred.

The efficiency of roentgen treatment as a means of producing the necessary changes in the ovary to bring about the menopause was demonstrated in the ovaries of one woman who came to autopsy three years after the treatment. Grossly, the ovaries were shrunken and fibrotic. Microscopically the follicles were destroyed, and there was connective tissue replacement. The report of Dr. Shields Warren follows:

> "The ovary presents the picture of an atrophic, postmenopause organ. The cortex is narrow, containing one or two scars but not follicles. In the medulla are numerous corpora albicantes. There is moderate hyalinization of the arteries."

The age of the patient, however, has some bearing on the ease with which the ovaries may be destroyed. This is to be expected since the follicles of the ovaries of the younger group are more numerous and probably more active than those of the older group. In general, it may be stated that large dosages should be employed to effect sterilization of the ovaries in the younger age group.

The fact that estrogens were recovered in every specimen of urine from the patients studied, including the surgical castrates, confirms the work of Frank and others;[13] La Roche and others;[14] Fluhmann;[15] Eng;[16] and others. Kurzrok,[17] Albright,[7] and others found no estrogens in the urine when follicle-stimulating hormone was present. With improved methods, however, in the extraction of the estrogens our findings can be reconciled to theirs, since the earlier methods were not delicate enough to detect minimal amounts of the estrogenic hormone. Hence, these findings suggest an extragonadal source of estrogens especially in the case of the surgical castrates. The adrenals are a possible source of estrogenic hormones if the ovarian follicles are completely suppressed, but proof for this is at present lacking.

These studies indicate that the menopause has occurred and can be produced artificially when desired, by the use of x-ray or radium, as efficiently as by surgery. It is our opinion that there is no essential difference in the menopause produced artificially from that which occurs spontaneously, with one exception; i.e. the severity of the symptoms and the rate at which it is produced and runs its course. Of the artificial methods surgery is the most rapid, with x-ray and radium following in the order named. Any of these methods have their analogies in the spontaneous menopause and eventually all lead to the same end.

CONCLUSIONS

1. The artificial menopause can be considered analogous to the spontaneous menopause, the major difference being the rate at which the climacteric is finally reached.

2. X-ray, if properly used with adequate-sized portals and dosage, is as efficient in producing the artificial menopause as surgery.

3. The success of castration with radiation depends to some extent upon the age of the patient.

4. Assay of the urine for follicle-stimulating hormone and estrogenic substances and endometrial biopsies give valuable information as to the effectiveness of radiation castration in the individual case.

5. Vasomotor symptoms of the climacteric are accompanied by hyperactivity of the anterior pituitary.

6. Elevated levels of follicle-stimulating hormone may be found in the absence of vasomotor symptoms, but on the other hand elevations in follicle-stimulating hormone are almost always detected in the presence of these symptoms.

7. Estrogenic substances exert an inhibiting effect on the action of the anterior pituitary gland.

8. There is probably an extragonadal source of estrogens.

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Ritala, A. M.: On the Inheritance of the Parents' Constitution by the New-Born Child, Ann. inst. obst. et gynec. Universitatis. **11:** 1, 1939.

Length and weight of body as well as head circumference of mother, father, and newborn child were studied by Ritala. In all, 12,860 body measurements of parents and newborn children were taken.

The weight and length of the newborn child proved to be considerably less, dependent upon the corresponding body measurements of the child's father, than upon those of the mother.

The results attained emphasize the comparatively great importance of heredity in opposition to the slight influence of environment or the mother's age, to which too great importance has been attached in the past. Besides inheritance, the sex of the fetus and the number of the mother's deliveries have been proved to exercise a decided influence on the body development of the newborn child.

J. P. Greenhill

THE RECOGNITION AND TREATMENT OF FETAL HEART ARRHYTHMIAS DUE TO ANOXIA*

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THE rate and rhythm of the fetal heart constitute the most satisfactory if not the only direct method for constant study of the physiology of the fetus during pregnancy and labor. Accurate interpretations of variations are as yet incomplete; nevertheless, auscultation provides evidence of impending fetal danger when marked arrhythmias are present. Fetal anoxia, infrequently recognized and rarely treated antenatally, can quickly produce grave fetal complications. The old therapeutic dictum "prophylaxis is the prime treatment" has not received significant consideration by obstetricians when signal variations of fetal heart rate foretell subsequent disaster. Careful and constant auscultation and recording of the fetal heart rate are the best criteria available for study of the unborn infant during labor.

Mayor[1] and Kergaradec[3] working independently first described the fetal heart sounds in 1818 and 1821, respectively, though Fasbender[2] gives credit to LeGoust in 1650. Kennedy,[4] Naegele,[5] and Hohl[6] first realized the prognostic importance of variations in fetal heart rate. Later Cummings[7] emphasized the danger associated with irregular or weak heart sounds. Von Winckel[8] in 1893 believed asphyxia imminent when the rate exceeded 160 or decreased below 100 and that expedient delivery was indicated. More recently other observers have arrived at similar conclusions. Included are Reed,[9] Sachs,[10] Frey,[11] Bartholomew,[12] Freed,[13] and many others.

Satisfactory reproduction and recording of the fetal heart rate is a comparatively recent accomplishment though first attempted by Hofbauer and Weiss[14] in 1908. The most recent study has been reported by Smith and Hervert[15] who have reviewed the literature and report the technical data concerning the study of the normal fetal heart.

APPARATUS AND METHODS

For the present investigation auscultation and recording of the fetal heart rate were accomplished with the endocardiograph;† a cardiograph devised for auscultation and recording of heart sounds, but readily applied to auscultation of fetal heart sounds with no significant change in apparatus. The sounds are picked up by a crystal microphone, amplified, and then may be heard by means of a binaural stethoscope or loud-speaker, or recorded on a moving strip of paper by a writing pen. The paper moves at a constant speed of one or two inches per second as desired. When at certain times the endocardiograph has not been available or desired, the fetal heart rate has been recorded by use of the head stethoscope or the weighted Leffscope[16] and a stop watch. During early first stage of labor, the fetal heart rate is observed every fifteen minutes or oftener if indicated; during the last portion of the first stage and the entire second stage, continuous auscultation is carried

*Aided by a grant from the Wisconsin Alumni Research Foundation, Madison, Wis.

†The endocardiograph is manufactured by the Endocardiograph Company, Milwaukee, Wisconsin.

out. Recordings are frequently taken and all significant changes of fetal heart rate recorded. The fetal heart rate was noted at the end of a contraction and during the middle and late interval. Because of occasional minor rate changes, 5 to 10 beats per minute, not infrequently noted in the early interval, the recorded rate was made during the late interval. The rate was obtained from 30 second counts, shorter periods of counting may lead to rather great errors because of the rapid rate of the normal fetal heart. When greater variation than 5 to 10 beats per minute was present, it was noted. Along with the usual obstetric abdominal and rectal examinations careful and frequent observations were made of the type and severity of the contraction, the duration of the contraction and the interval between contractions. Furthermore, all cases were personally observed and recorded throughout, the importance of this is obvious but actually becomes a necessity during the period of continuous auscultation when readings require the entire attention of one individual. The anesthetic agents and gases were administered by members of the Department of Anesthesia, all of whom are trained, experienced anesthetists. The method of oxygen administration depended upon anesthetic technique. Any of the common standard techniques is satisfactory, provided adequate concentrations of oxygen reach the alveoli of the lung.

As has been mentioned, the slowing of the fetal heart rate has long been considered a sign of developing fetal asphyxia. Likewise, knowledge concerning the need for adequate oxygenation of the fetus to prevent apnea at time of delivery is of long standing and many have recognized the fact that oxygen could be administered to the mother in order to reach the infant.[17-20] To Waters and Harris[21] must go the credit for emphasizing the fact that anoxia of the fetus can be recognized by change in the fetal heart rate and successfully treated by oxygen administration, thereby forestalling development of respiratory depression due to anoxia.

The importance of this observation has never been fully appreciated, and for this reason we have added a series of carefully studied cases, recently observed, which demonstrate the changes in fetal heart rate due to anoxia. With the perfection of auscultatory and recording devices we can now present objective evidence of these arrhythmias. It is not uncommon to observe term pregnancies, with fetal arrhythmia definitely due to anoxia. Eight cases have been chosen because each demonstrated slowing of the fetal heart due to anoxia and the therapeutic response to specific therapy, oxygen. Irregularities of fetal heart rate due to all other causes have been deliberately deleted from this report and will be considered in subsequent publications. This includes the other very important factor of asphyxia, carbon dioxide.

RESULTS

Table I summarizes the data regarding the condition of the patient at the time of the onset of fetal heart changes. From this it can be seen that many factors have been eliminated as individually etiologic, such as position, presentation, state of membranes and type of contractions and, furthermore, that anoxia can be present

TABLE I. OBSTETRIC STATUS AT THE TIME OF ONSET OF ANOXIC SLOWING OF FETAL HEART AND THE RESPONSE TO OXYGEN THERAPY

	POSITION	STATION	DILATATION	MEMBRANES RUPTURED	TYPE OF CONTRACTIONS	DURATION OF CONTRACTIONS (SEC.)	MINUTES BETWEEN CONTRACTIONS	MATERNAL CYANOSIS	SPONTANEOUS RESPIRATIONS	ASPHYXIA	CORD AROUND NECK	FETAL HEART RATE					RELATION OF ONSET TO ANALGESIA
												BEFORE ANOXIA	WITH ANOXIA	DURATION OF SLOWING (MIN.)	AFTER OXYGEN THERAPY	RECOVERY (COMPLETE) TIME (MIN.)	
1—UG	S.L.T.	−1	6	Yes	Str.‡	60	3	+	Yes	No	No	156	68	15	150	15	Before
2—EE	L.O.A.	+3	C*	No	Str.	60	1	−	Yes	No	Yes	140	70	8	135	8	With
3—SE	L.O.A.	0	C	No	Mod.‡	45	2	+	Yes	No	No	136	110	4	140	8	After
4—RH	L.O.A.	+2	C	Yes	Str.	60	1½	−	Yes	No	Yes	116	98	13	120	10	With
5—VA	R.O.P.	0	0	No	—	—	—	+	Yes†	No	No	142	96	15	140	7	With
6—RN	L.O.A.	+1	4	Yes	Mod.	45	3	−	Yes	No	Yes	144	110	10	130	5	After
7—EF	S.L.A.	+3	C	Yes	Str.	50	2	−	Yes	No	No	140	110 to 130	15	130 to 140	15	With
8—EW	L.O.A.	+1	8	Yes	Mod.	50	3	−	Yes	No	No	142	100 to 134	8	136 to 144	12	With

*C, signifies complete dilatation of cervix.
†Patient not in labor at this time but delivered three days later.
‡Str., strong contractions. Mod., moderate contractions.

whether the patient is in labor or not. From this we do not mean to say that any of these given factors is not without effect in certain instances or entirely etiologic at other times.

Table I also summarizes the gross changes found in the fetal heart rate, the duration of arrhythmia before and after oxygen therapy, and the condition of the infant at the time of delivery. In order to eliminate any cases showing sudden transient changes in fetal heart rate which frequently correct themselves, it has been a rule to allow the slowing to persist for a minimum of ten minutes, if possible without danger to the fetus, or through at least three-interval periods between contractions. The time interval given for complete recovery signifies the time elapsed in minutes before recovery had reached its maximum point, which in most cases was a return to the original rate. The effect of oxygen, as will be seen later, can frequently be demonstrated within three to five minutes, the longest latent period was eight minutes. In every case respirations and cry were spontaneous, and there were no signs of anoxia or apnea at birth.

A short summary of the most significant and illustrative cases will serve to emphasize the various factors involved in producing fetal anoxia with arrhythmias and recovery after oxygen therapy.

CASE 1.—V. G., a very obese multipara, 40 years of age, weighed 256 pounds. Hypertensive heart disease was present with a blood pressure of 180/110. At bed rest she was neither dyspneic nor cyanotic. However, on very slight exertion dyspnea became marked. Labor was slow and difficult because of breech presentation and marked angulation of the uterus through a ventral hernia. Onset of slight dyspnea was noted after four hours of labor; however, there was no change in fetal heart rate which persisted at 150 to 160 for the following five hours. At this time dyspnea became marked and slight cyanosis could be seen. The fetal heart rate decreased to 135 and then to 70. This rate persisted constantly for over ten minutes. Cervical dilatation was 6 cm. and the breech was not engaged. At this time the patient was allowed to breathe a high concentration of oxygen through a face mask. Within three minutes the rate had increased to 95, after five minutes the fetal heart rate was 120, after ten minutes was 135, and after twenty-five minutes 148 (Fig. 1). Similarly there was improvement of maternal dyspnea and cyanosis after ten minutes of oxygen therapy. After twenty minutes respirations were normal, and after thirty minutes the maternal pulse rate had decreased from 120 to 100. Good pain relief was obtained from nitrous oxide oxygen and cyclopropane analgesia and no further slowing of the fetal heart rate occurred. The cervix was allowed to dilate, and delivery was accomplished two hours after the original onset of fetal heart slowing. The infant was in good condition at birth.

CASE 2.—E. E. The fetal heart rate in this young primipara during the last part of the first stage and the early second stage of labor remained within the limits of 140 and 148. It was unaffected by nitrous oxide (70 per cent) oxygen (30 per cent) analgesia for thirty minutes. At this time due to increased severity of pains, the nitrous oxide was increased to about 85 per cent. This diminution of oxygen supply plus the increased need due to muscular effort in bearing down caused a slowing of the fetal heart rate within four minutes to 120, and within eight minutes to 70 (Fig. 2). At this point, without any other change in obstetric or anesthetic procedures, the patient was given oxygen during the interval between contractions. Within two minutes the rate reached 90 at the end of a contraction. After six minutes the rate was 105, after eight minutes 135, with only a very slight slowing to 128 immediately after a contraction. This improved rate persisted and spontaneous delivery of a normal infant in good condition followed one-half hour later.

CASE 3.—S. E., a primipara, in the second stage of labor, was being examined under cyclopropane-oxygen anesthesia. The fetal heart rate before anesthesia was constant within a range of 132 and 136. During the first five minutes of anesthesia, it remained between 136 and 140 (Fig. 3). At this time large amounts of mucus accumulated, causing respiratory obstruction with rather marked cyanosis. Fetal heart rate reached a low of 110, at the time the respiratory obstruction was corrected. The rate improved to 126 within eight minutes and after eleven minutes

was 140. Later cyanosis again followed obstruction, immediately the fetal heart rate decreased from 140 to 120. Correction of the obstruction relieved the cyanosis and the fetal heart rate increased to 136 within five minutes. The rate remained constant at 130 to 136 for twenty minutes until delivery.

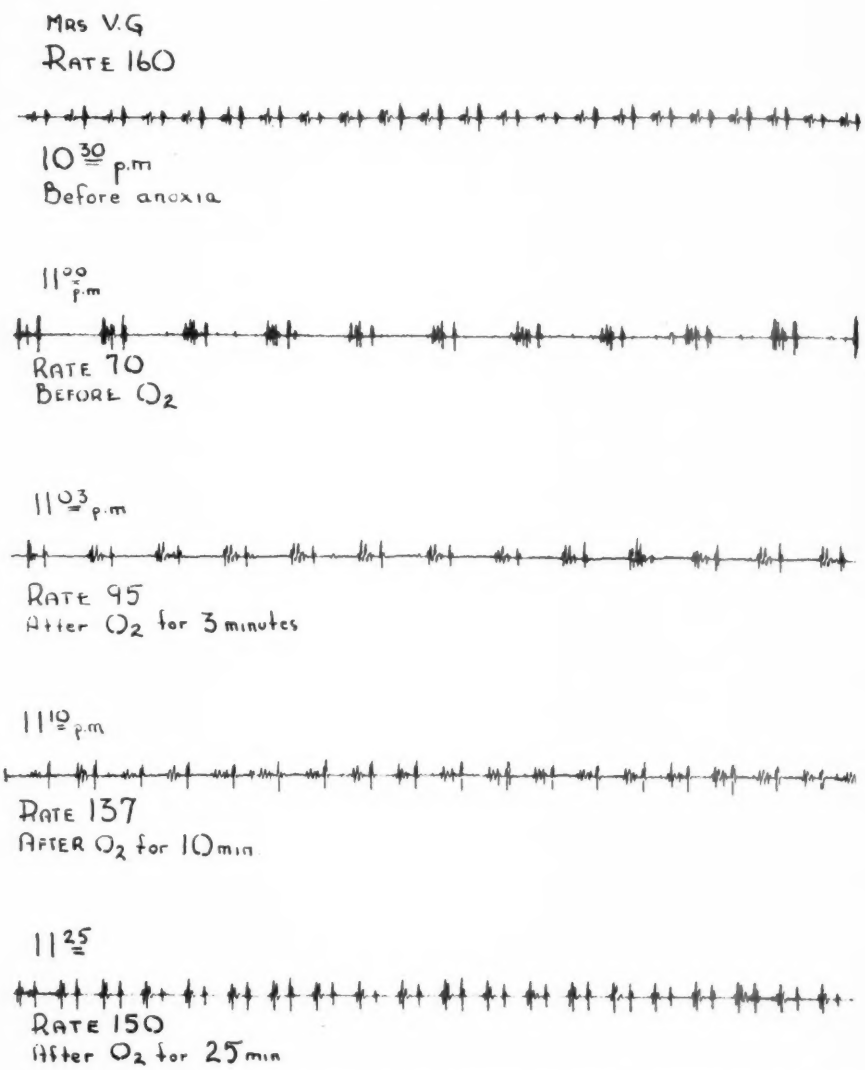

Fig. 1.—Normal fetal heart rate of 160 followed by marked slowing to 70 due to anoxia. Response to oxygen present in three to five minutes with complete recovery in twenty-five minutes.

CASE 5.—V. A., a primipara, at term, not in labor, was to be examined under anesthesia. Nitrous oxide was chosen to demonstrate the slowing of fetal heart rate that follows use of too high concentrations of nitrous oxide and insufficient oxygen (Fig. 4). Normal fetal heart rate was 142, within ten minutes the rate had decreased to 96 during period of induction of anesthesia, after stabilization an optimum rate of 105 was obtained under nitrous oxide anesthesia, slight maternal cyanosis being present at this time. With addition of oxygen and change to another anesthetic agent, permitting greater concentrations of oxygen, the fetal heart rate returned to a normal rate of 140.

CASE 7.—E. F., a primipara, with breech presenting, was in the second stage of labor. A slowing of fetal heart rate was noted shortly after nitrous oxide analgesia was instituted. Within ten minutes the rate was 100, immediately after a contraction, and the slowing persisted throughout all but the final fifteen or twenty

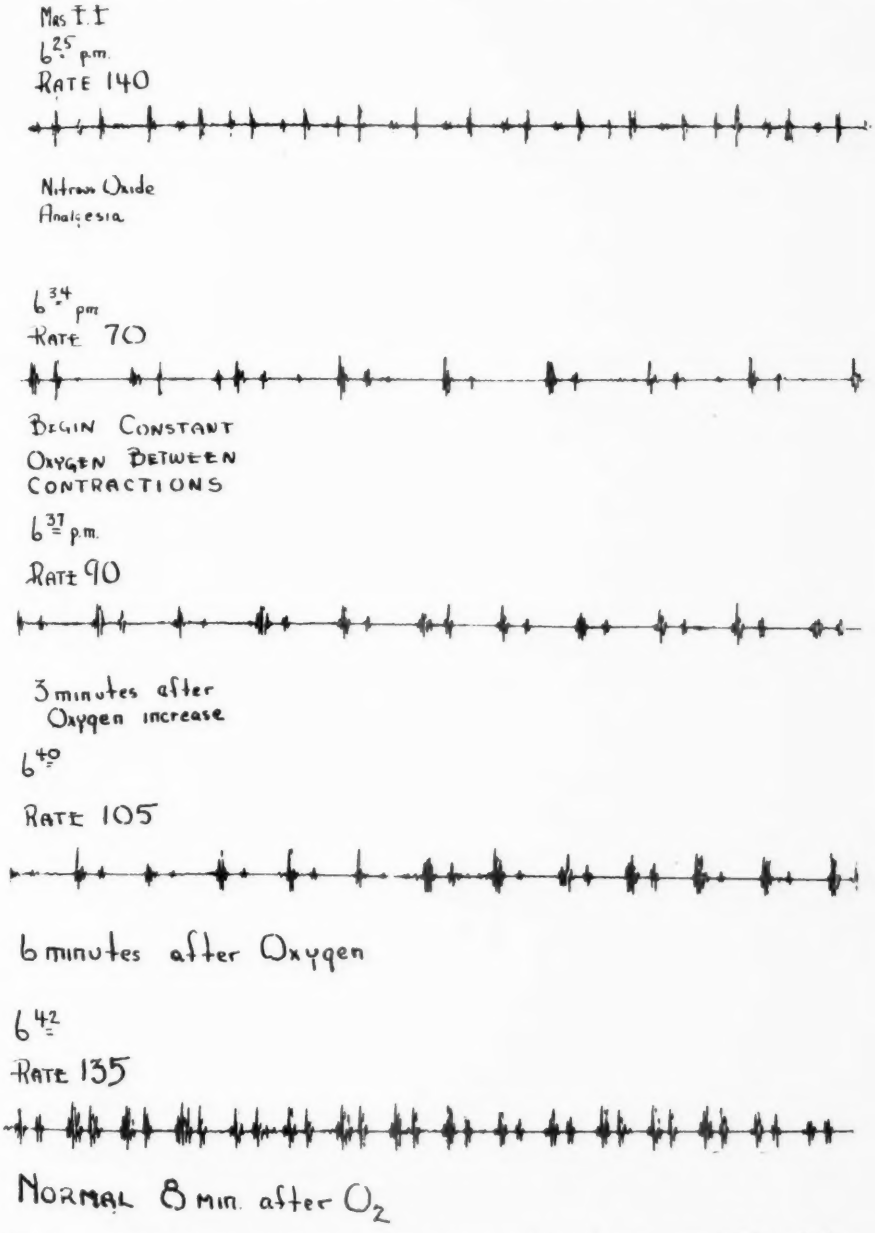

Fig. 2.—Slowing of fetal heart rate under nitrous oxide analgesia corrected by administration of oxygen during the interval between contractions.

seconds of the two-minute interval, when it rose to 130. At this time oxygen was given between contractions. Within fifteen minutes, the rate, while still 100 immediately after a contraction, recovered to 135 within one minute, leaving a normal

rate for the entire remaining minute of the interval. The infant was born in good condition twenty minutes later.

DISCUSSION

The occurrence of arrhythmias of the fetal heart during labor is far more frequent than is generally believed. This is probably due to infrequent and inaccurate auscultation. Of these arrhythmias, due to

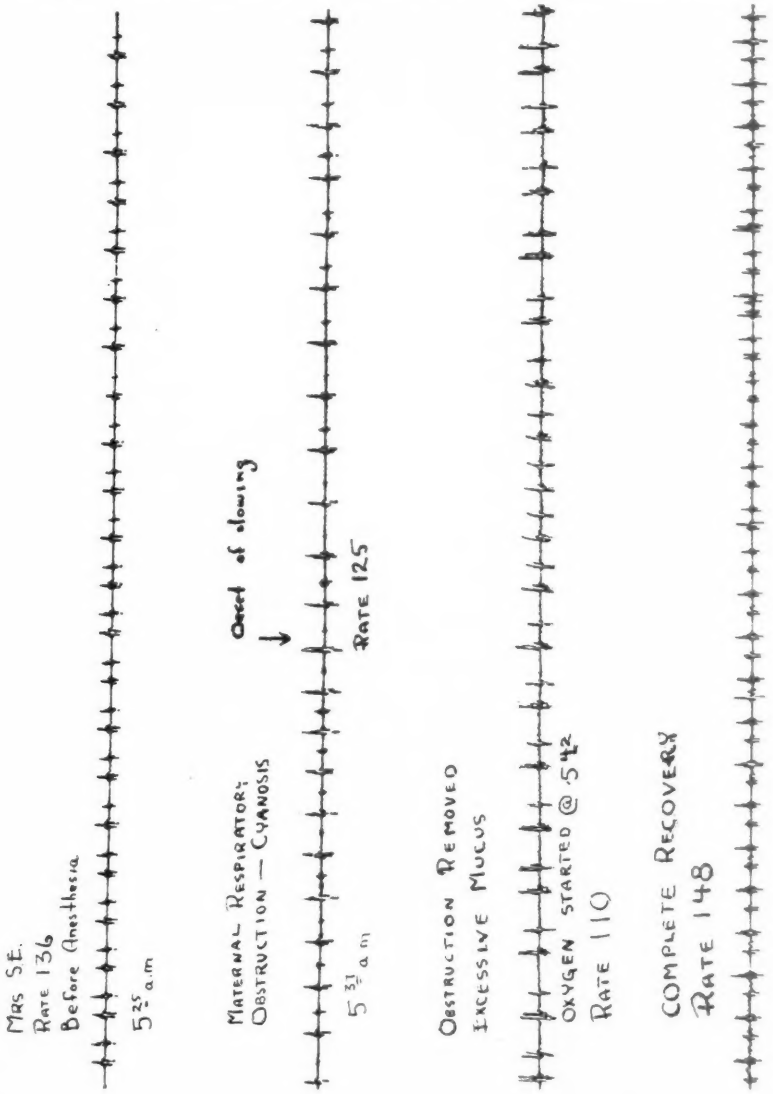

Fig. 3.—Slowing of fetal heart rate from anoxia due to maternal respiratory obstruction by excess mucus. Aspiration of mucus and establishment of good airway resulted in recovery.

anoxia in utero, those that can be corrected by administration of oxygen to the mother constitute a far greater group than many obstetricians and anesthetists realize. From the vast literature of recent years, several definite clear-cut facts have been determined concerning the signs and sequelae of oxygen want. In adults mild degrees of anoxia are followed

by acceleration of the pulse and respiration. If the anoxia persists or increases, the point of "oxygen crisis" is reached. Schmidt[22] calls the subsequent period the "reversal" in which the heart rapidly slows to

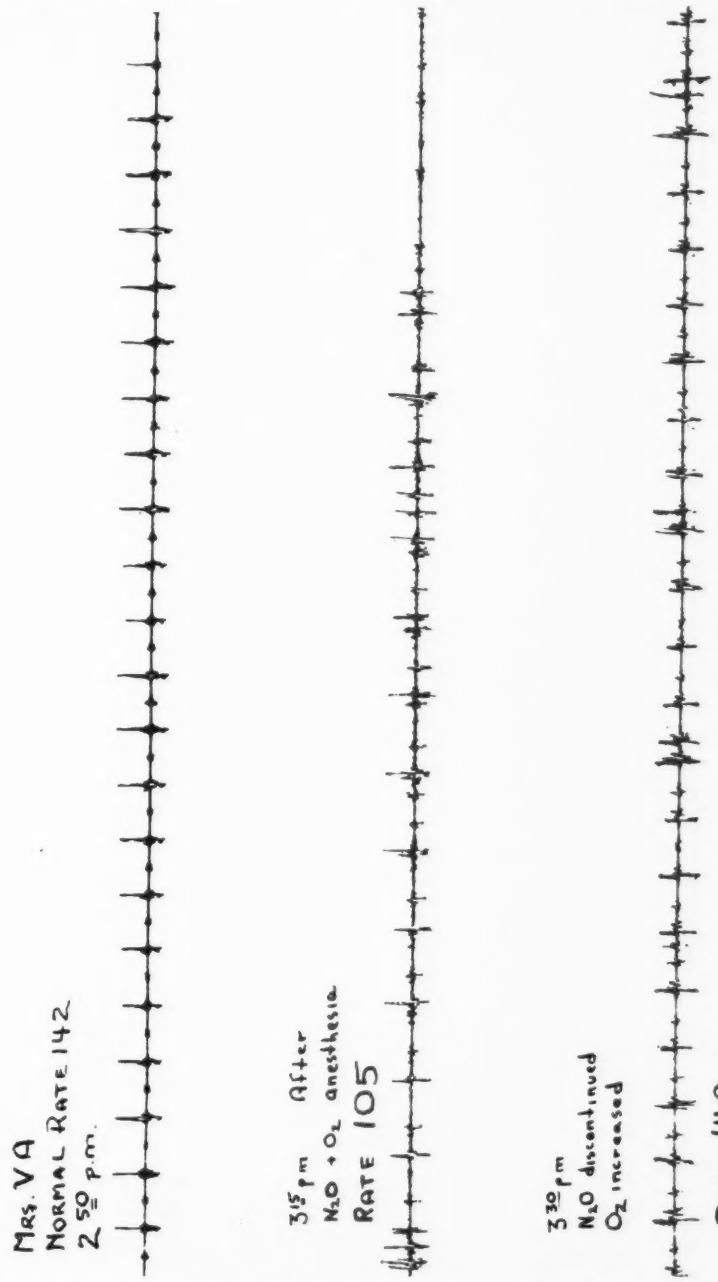

Fig. 4.—Complete anesthesia (first plane) with nitrous oxide required the reduction of oxygen to a point below physiologic needs with resulting anoxia and slowing of the fetal heart rate.

about 40 or 45. Vagal stimulation is apparently the cause for the slowing of the heart rate. Persisting anoxia in the adult is followed by serious cerebral damage as noted by Yant and others,[23] Courville[24] and

Schreiber[25] who also describe "devastation areas" in the cortex of infants dying of asphyxia.

Most authors state that the first sign of fetal asphyxia is an acceleration of the fetal heart rate and as asphyxia deepens the rate slows markedly, just as has been described for adults. We have failed to note acceleration of the heart rate in any of the cases of this series. Just why the fetal heart does not consistently respond to anoxia by acceleration is not known. Perhaps it is masked by other factors such as the rapidity of the development of the anoxia or the degree of anoxia present. Snyder and Rosenfeld[26] discovered that intrauterine respirations of the fetus were not stimulated by mild anoxia as in the adult individual. The mechanism involving the fetal heart rate and respiratory rate may be similar in nature, for we know that both respiratory rate and pulse rate are stimulated by mild degrees of anoxia in the adult.

In the same year that Waters and Harris[21] reported successful therapy of anoxic infants in utero with slow fetal heart rate, Rech[27] reported that he had given patients, in labor, increased concentrations of oxygen without effect on fetal heart rate. He also reported that exposure to a low oxygen content of inspired air for one and one-half minutes was without effect on the fetal heart rate. The development of significant anoxia in utero in our experience is not ordinarily accomplished in the short time of one and one-half minutes. In Case 3 rather marked maternal oxygen want was present for five minutes before effect was noted on the fetal heart rate. This lag in response is not remarkable when the complexity of the transporting system is considered. Involved are the circulation time through the uterus, the oxygen saturations in the placenta, and the circulation time of the fetus. The latter alone has been found to be about forty seconds.[36]

There are two broad factors involved in the production of anoxia of the fetus, maternal failure to supply oxygen, and failure of the fetus to receive a proffered supply.

1. *Failure of Maternal Supply.*—This includes a list so great that its limits would be bounded only by the ingenuity of the enumerator. For a general classification of anoxia the accepted group suffice: (1) Anoxic, (2) stagnant, (3) anemic, and (4) histotoxic. Yet it must be appreciated that nearly every case under consideration may, and usually does, involve a combination of several of these factors.

Failing or inefficient respiration (anoxic anoxia) probably represents the major etiologic factor in most of these cases. The significance of the relatively low oxygen concentration of anesthetic mixtures of nitrous oxide has been discussed for many years. Positive proof that anoxia follows the use of certain mixtures of nitrous oxide and oxygen was revealed by Leake and others,[28] Waters and others.[30] In Eastman's[31] studies definite fetal anoxia was produced by administration of nitrous oxide oxygen in concentrations of 90:10 for longer than five minutes. Danforth and Davis[18] noted a slowing of the fetal heart rate during deep gas (nitrous oxide oxygen) anesthesia which resembled those heard in asphyxia. Smith[32] reported fetal anoxia during delivery under cyclo-

propane anesthesia when maternal oxygenation was good. During the past year, our data, as yet insufficient and inconclusive, tend to confirm this observation as demonstrated by a slowing of the fetal heart rate in deeper planes of cyclopropane anesthesia, but not so with ether. Slowing of the fetal heart rate under anoxic conditions associated with nitrous oxide oxygen anesthesia can be readily and repeatedly demonstrated and recorded (Fig. 4).

Fetal anoxia produced by obstruction to the maternal respiratory passages should be prevented or immediately relieved by correction of such impediments. This was very vividly demonstrated and recorded during our studies (Fig. 3) and has been observed many times. The presence in the respiratory passages of mucus or gastric contents from emesis frequently causes obstruction. Likewise does the relaxation of lingual and pharyngeal musculature, because of large doses of analgesic drugs or anesthetic agents, cause respiratory obstruction and maternal anoxia. Correction of the obstruction and the addition of oxygen under these circumstances will usually quickly restore the fetal heart rate to normal.

Drug anoxia as described by Schreiber[33] included drug toxicity and sensitivity. Alveolar oxygen concentration can be reduced by drugs as has been shown by Waters and his associates.[30] They describe actual minute volume respiration reduction as observed after administration of opiates and barbiturates, due to their respiratory depression. This effect is reflected in fetal heart rate, a study which is as yet under investigation.

Stagnant anoxia due to failing or inefficient circulation, a situation occurring in cardiac conditions, was demonstrated by Case 1 (Fig. 1). Anemic anoxia was not active in these cases, yet it can be a potent factor in cases of hemorrhage and shock. The histotoxic factor is still poorly understood.

2. *Failure of Fetus to Receive Oxygen.*—Assuming that the maternal blood stream is well saturated with oxygen, many factors prevent the fetus from obtaining it.

a. *Disturbances of Placental Circulation:* This may be due to excessively long or frequent contractions. Notably anoxia is known to follow tetanic or long-sustained contractions due to the use of oxytocics. Disturbance of circulation by premature separation of the placenta and placenta previa are common. Richardson[34] describes first an acceleration and later a slowing of the fetal heart rate in premature separation of the placenta due to a disturbance of the oxygen carbon-dioxide balance, believing that over one-half separation causes a slowing and over three-fourths separation gives a rate of 70 to 90 and frequently causes death. Clifford[35] studied the amount of intrauterine asphyxia following placenta previa and found it to be so great that 11 infants died after delivery, due to cerebral changes inflicted by the oxygen want before delivery. He did not note any changes in fetal heart rate.

b. *Cord Entanglement and Prolapse:* These constitute the most frequent causes of intrauterine asphyxia as quoted by the Bureau of

Census. With complete obstruction of the cord, asphyxia is inevitable; not so, however, with intermittent cord pressure and cord entanglement. In these cases, the obstruction may be complete at the time of uterine contractions, giving a slow fetal heart rate during the interval. If oxygen is given in large amounts between contractions, the enriched maternal blood supply is capable of restoring the infant, and improvement is noted. This was noted in Case 8 in Table I. While it is not advisable to delay treatment in cases of cord prolapse, nevertheless high concentrations of oxygen should be given while preparing for expeditious delivery.

Recognition of intrauterine anoxia is generally dependent on a slowing of the fetal heart rate, either in the form of a rather sudden change of 25 or more beats per minute or a persistent slowing below 100 and 110. This is of greater significance, should any of the previously mentioned etiologic factors be present. The diagnosis may be considered positive, should the therapeutic response to oxygen be obtained. Obviously the converse is not true, for all cases of fetal anoxia do not respond to maternal oxygen therapy.

In general, the response to oxygen therapy is rapid and at times dramatic. In every case of the series, there was improvement within five minutes after therapy was begun and maximum recovery was reached within twelve to twenty minutes. This fact is of clinical importance, because on most obstetric floors, at least ten minutes elapse before the patient can be prepared for immediate delivery, should it be possible and elected because of slowing of the fetal heart rate. During this time the anesthetist can be giving the therapeutic test of oxygen. Improvement should be noted within ten minutes after administration and frequently will be seen within five minutes. Failure of any response within ten minutes is significant, and a persistent fetal heart rate below 100 indicates that response to oxygen will probably not be seen and delivery should not be delayed. If delivery is impossible consideration should be given to deep anesthesia with simultaneous continuation of oxygen concentration at a high level. The fact that nitrous oxide was involved in several of these cases does not condemn the use of the gas as an analgesic agent or even as an anesthetic agent for a short period of time. Of great importance is the fact that high concentrations of oxygen may be given to the patient during the intervals between contractions to relieve a fetal anoxia that may occur during the fifty to seventy seconds of nitrous oxide analgesia.

SUMMARY

The literature is replete with methods and devices to treat asphyxia of the newborn. The value of this therapy cannot be disregarded or minimized and yet in many cases the opportune time for therapy has passed and irreparable damage to the central nervous system is the unfortunate result. Variations of the fetal heart rate have long been ascribed to asphyxia and the recommended therapy has been immediate delivery. The early recognition of impending fetal asphyxia can be

determined by continuous or at least very frequent auscultation of the fetal heart sounds. Institution of specific therapy, oxygen, at this time will in many cases either partially or completely restore the fetal heart rate to normal and successfully combat the anoxia. The response to oxygen therapy should be noted within ten minutes and frequently is apparent in less than five minutes. If after fifteen minutes of therapy no improvement is noted, it may be assumed that oxygen will be of no value. The time of preparation of a patient for operative delivery is usually more than ten minutes and this can be carried out while the oxygen is being given; thus no hazard is created for the infant. Frequently the improvement in the fetal heart rate will obviate the necessity of exigent operative delivery and its danger to mother and infant.

CONCLUSIONS

1. Impending fetal asphyxia can be determined by careful frequent auscultation during active labor.

2. A method for continuous auscultation and recording of fetal heart sounds is described.

3. Fetal heart arrhythmia due to anoxia is described and the response to oxygen recorded.

4. The etiologic factors of fetal anoxia are discussed.

5. Early recognition of fetal anoxia and treatment by maternal oxygen therapy will prevent many cases of asphyxia neonatorum.

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FURTHER STUDIES ON HORMONE EXCRETION DURING THE MENSTRUAL CYCLE*

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INFORMATION concerning the daily hormone excretion of the normal human female is valuable for several reasons. Such knowledge contributes to our understanding of the endocrine control of reproductive processes. Before abnormalities can be diagnosed and logical endocrine therapy be instituted, normal values must first be established. The determination of the time of ovulation is a matter of practical importance to many, and the method of urine assays is a promising one in this connection. This paper, which presents the results obtained from the daily assay of urine from 29 cycles, of 5 subjects, for both estrin and gonadotropin, is submitted as a contribution to the slowly accumulating mass of knowledge concerning these problems. It is recognized that much more information, from many sources, must be secured and synthesized before secure conclusions can be drawn.

EXPERIMENTAL

At a recent Federation meeting Dr. Pincus pointed out that much research fails to realize its maximum value because workers have used variations in technique which make direct comparison of results impossible. This criticism is especially valid in such studies as the present one, where the problem's final solution must come from work done by many people. For this reason, and because the methods used have been satisfactory, they are described in some detail.

A. Methods.—Complete twenty-four-hour specimens were collected, chloroform being used as preservative. After filtering, acetic acid was added to a pH of 4.5. Twenty cubic centimeters of a freshly prepared 10 per cent tannic acid solution was added per liter of urine, the mixture was well shaken and permitted to stand overnight in the refrigerator. The precipitate was removed by centrifuging, washed once with 95 per cent alcohol and 4 times with 80 per cent alcohol, centrifuging each time, and finally washed on filter paper with acetone. The precipitate was dried and assayed for gonadotropin. This is essentially the method of Levin and Tyndale.[1]

The alcohol and acetone washings, as well as any excess chloroform used as preservative, were evaporated to dryness and the residue returned to the day's urine from which it came. This urine was hydrolyzed for two hours with hydrochloric acid (100 c.c. con. HCl per liter urine), cooled, and extracted with chloroform. The latter was added to corn oil, boiled off, and the corn oil assayed for estrin.

For the assay of gonadotropin, female rats twenty-six days old at the time of first injection were used. The precipitate was ground in saline so that the total dose to be given each rat was present in 1.5 c.c. Injections were made once daily for three days (0.5 c.c. per injection) and the animals sacrificed at the end of one hundred hours. The uteri were carefully dissected, pressed between moist filter paper and weighed. Except where otherwise noted, the dose administered in this study was the equivalent of three hours' urine excretion per rat. This permitted

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the use of 8 rats per day's urine, which, while perhaps still not enough to justify use of the word "assay," is at least a great improvement in sensitivity over the ovarian weight method. There is no correlation between volume of urine, nor weight of precipitate, and activity; it is therefore necessary to base results on "hours of excretion." No difficulty whatever was experienced with toxicity of precipitates; of the thousands of animals used in this study not one died as the result of injection.

In the assay of estrin, the chloroform was placed in such volume of corn oil that 0.5 c.c. contained the required dose. Except where noted, the curves are based on a dose of one hour's urine excretion per rat. This permits the use of 24 animals per day's sample, sufficient for reasonable accuracy of results. The test is the well-known vaginal method of Allen and Doisy. The sensitivity of the colony was frequently checked with International Standard estrone.

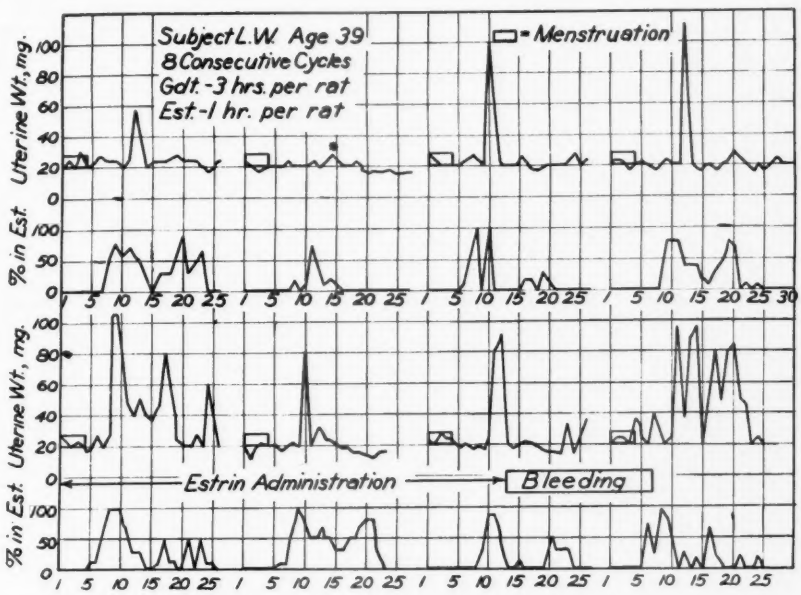

Chart 1.

B. Results.—These are presented in Charts 1 to 4. Each chart includes 8 cycles, 4 in the upper half and 4 in the lower, the upper line of each half representing the gonadotropic assay in terms of average uterine weight, and the lower, the estrin assay for the same cycle, in terms of percentage of animals showing a positive response.

The subject (Chart 1), L. W., aged 39 years, married, mother of 3 children, had a normal gynecologic history. The first four cycles were normal, considering the second, possibly anovulatory, as normal. (The question of anovulatory cycles is discussed below.) During the last four cycles she subjected herself to estrin administration. This experience will be more fully described elsewhere but a few points may be noted here. During the first of these cycles the gonadotropic output was increased, which was perhaps to be expected on the basis of a primary stimulating effect of estrin upon the pituitary. The second and third cycles were normal; since the dosage of estrin was small (only 0.04 mg. estradiol daily), no demonstrable inhibition of the pituitary was produced. However, an alarming episode of bleeding occurred, as noted on the graph, and the administration of estrin was discontinued. The apparent excessive activity of the pituitary during the fourth cycle may be explained as a release from a certain degree of pituitary inhibition. These explanations are, of course, speculative, but are in line with theories of ovary-

pituitary relationship based on animal experimentation. It should be added that menstrual cycles over the succeeding two years have been normal; therefore the bleeding noted could not have been related to the onset of the menopause.

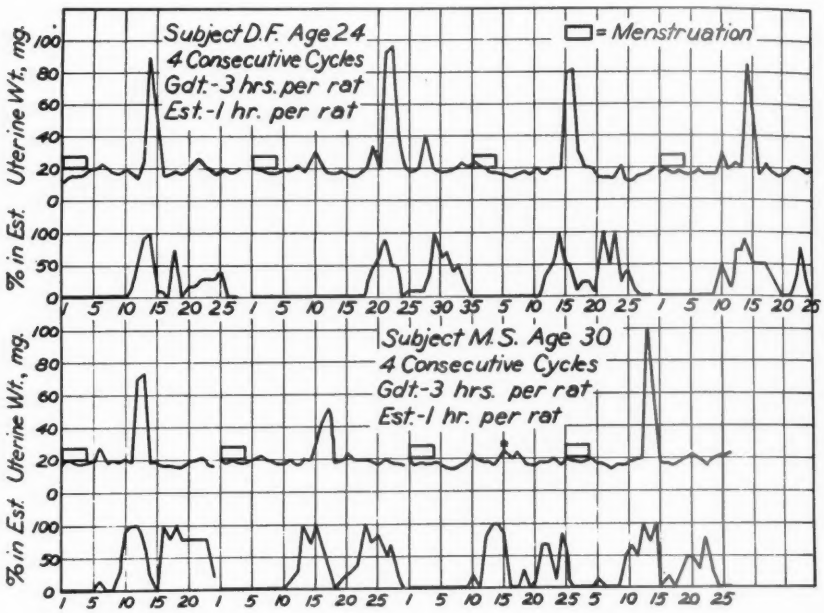

Chart 2.

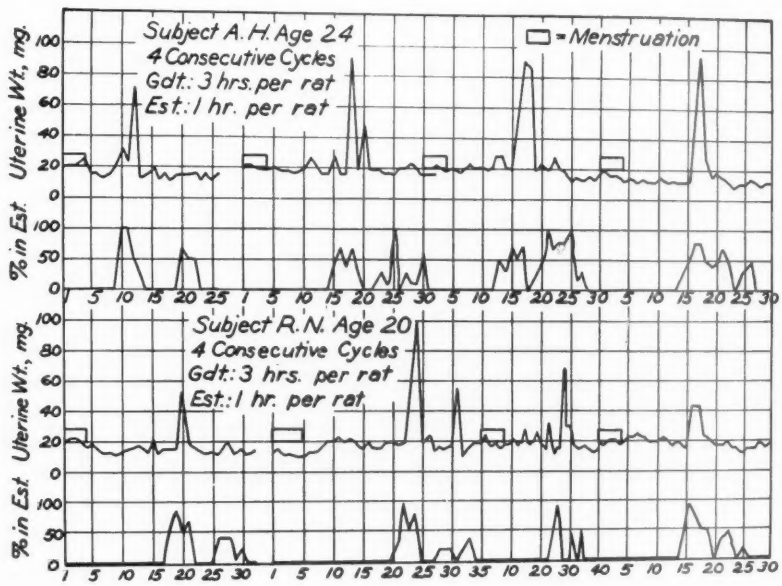

Chart 3.

In the upper half of Chart 2, four cycles of Subject D. F. are illustrated and in the lower half, the same number for Subject M. S. Both are single women with normal gynecologic histories. The third cycle of M. S. is presumably anovulatory, the others normal.

The upper half of Chart 3 is devoted to Subject A. H. and the lower half to Subject R. N. Their cycles are continued on Chart 4, there being 6 consecutive cycles for the first subject and 7 for the second. Both are single young women with normal histories. Each shows one presumably anovulatory cycle, the rest being normal.

Chart 4 shows the results found when the last cycle of A. H. and the last two of R. N. were repeated, the dose of each hormone being doubled. The original graphs are re-drawn with the results on double dosage indicated by the broken lines.

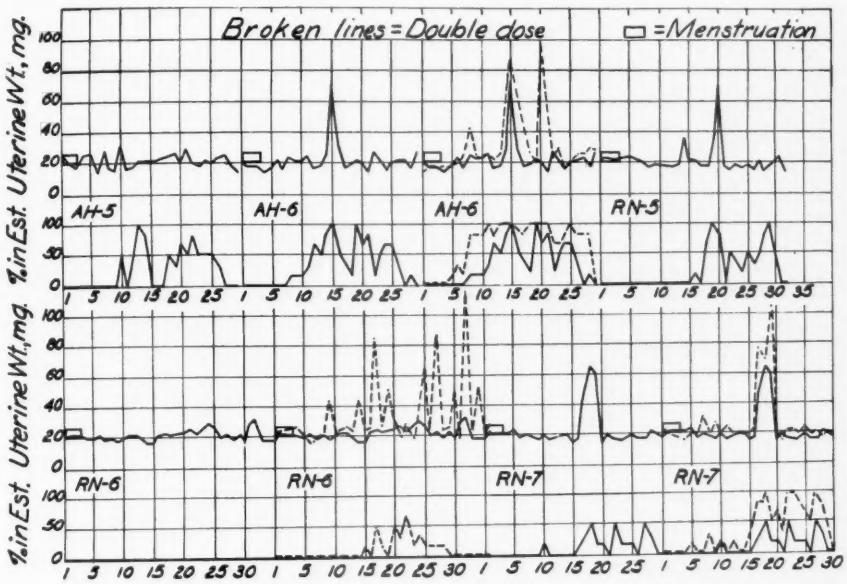

Chart 4.

DISCUSSION

A. Time of Ovulation.—It is unnecessary to review here the extensive literature on this subject. Suffice it to say that evidence from all sources is in general agreement that this event occurs some ten to sixteen days prior to the onset of the next menstruation. Here we are concerned primarily with the question of the practicability of the urine assay method, which, although tedious, has the advantage of making small demands upon the subject and is therefore useful for long-time studies. It is, of course, an indirect method and, as is true of all indirect methods, such as uterine motility, vaginal smear, etc., there is no certainty of the relation of the observed phenomenon to ovulation. The only test for the validity of any such method therefore is its comparison with results achieved with others. That the agreement is good is indicated by Table I.

It happens that Subject L. W. has relatively short cycles, averaging 26 days, while those of R. N. average 34 days (one of 42 days), yet the peak occurs approximately the same number of days before the ensuing menses in both cases. This supports the view held by most workers that the luteal phase of the cycle is of relatively fixed duration.

TABLE I

SUBJECT	TOTAL CYCLES	POSITIVE CYCLES	DAYS PRECEDING MENS. OF GONADOTROPIN PEAK	PRESUMABLY ANOVULATORY
L. W.	8	7	13-15-16-16-14-15-14	1
D. F.	4	4	13-14-14-14	0
M. S.	4	3	12-13-13	1
A. H.	6	5	13-15-15-15-16	1
R. N.	7	6	13-12-14-14-12-12	1
	29	25	Min. 12; Max. 16; Av. 15.1	4

In a previous study[2] I reported a series of 50 cycles in which the daily gonadotropic output was tested. In that study the criterion of activity was increase in weight of the rat's ovaries. In many cases more than one gonadotropic peak occurred during a given cycle. In the present study, excluding L. W.'s cycles influenced by estrin administration, this irregularity was not present. No doubt the explanation lies in the greater sensitivity of the uterine weight method, which permits the use of a smaller dosage and a larger number of animals. If, as seems likely, the pituitary maintains some degree of gonad-maintaining activity throughout sexual life, the problem becomes one of determining peaks in its secretory activity. For this, the injection of large amounts of material into a few animals is unsatisfactory. On the basis of the present data, there is no evidence for multiple ovulation. The final answer to this, as to many related questions, must await further study.

There remains the question of interpretation of those cycles in which no gonadotropic peak occurs. In the paper mentioned, 3 of the 50 cycles were of this character; in this study, 4 of 29. If the sudden output of a relatively large amount of gonadotropin indicates the operation of a mechanism resulting in ovulation, then its absence should mean the failure of ovulation to occur and these cycles may be considered anovulatory. An interesting, probably meaningless, point is that six of the seven cycles of this character occurred in the spring.

Summarizing, it may be said that with the method and dosage used, a considerable degree of uniformity in results was obtained, in that 25 of 29 cycles gave positive responses between twelve and sixteen days preceding menstruation; the other four no reaction, being presumably anovulatory. Further, that the use of a more sensitive method and larger numbers of animals has eliminated the frequent occurrence of multiple peaks in gonadotropin output previously noted. Finally, that, in my opinion, the urinary assay method, with due regard to details of dosage and technique, is a valuable one, but that much further data must be obtained before its reliability will have been sufficiently established to warrant secure conclusions, from it alone, as to the time of ovulation.

B. Levels of Hormone Excretion and Time Relationship.—In the preceding paragraphs the gonadotropic output was considered. As a test for ovulation time, a dosage of three hours' urinary excretion per rat appears satisfactory. The uterine reaction obtained is equivalent to that given by 0.5 to 1.0 international units of either chorionic or pregnant mare's serum gonadotropin. The total excretion per peak therefore equals from 4 to 16 I. U. The question arises as to the secretory

activity of the pituitary at other times during the cycle. The difficulty in determining this is that the amount of gonadotropin in each day's output is so small that with present methods it is impossible to assay it at two or three dosage levels, using a sufficiently large number of animals on each dose for the results to be meaningful. We did repeat three cycles, A. H.-6 and R. N.-6 and 7 (see Chart 4), on double the original dose, i.e., six hours' excretion per rat instead of three. Half the urine having been used on the original dose, only 2 rats could be used on the larger, and the results cannot be considered quantitative. For A. H.-6 the double dose curve shows two additional peaks, R. N.-6 a saw-tooth effect with many positive responses and R. N.-7 a duplicate of the original curve. While no conclusion as to amount or regularity of secretion is possible, activity of the pituitary, as indicated by the appearance of its secretion in the urine, does occur at other times than the mid-interval.

The excretion of estrin during the menstrual cycle has been investigated by a number of workers, Gustavson and others[3] having contributed probably the most thorough study. They found two peaks in estrin excretion as typical of the normal cycle, the amount at the peaks being equivalent to 600 to 800 I. U. In the present study a somewhat simpler method, both of preparing the sample and indicating the results was used, the results being shown simply on the basis of the percentage of animals responding positively to a dose (as a rule) of one hour's excretion per rat. Exact quantitative comparison is not possible but peaks showing 100 per cent positive responses are equivalent to an output of approximately 800 I. U. The possibility of estrin excretion at a lower level during phases of the cycle other than the normal waves was considered and in the three duplicate cycles shown in Chart 4 the assay was repeated using a dose of two hours' urine per rat. As before, fewer animals (6 only) could be used on each day's sample. For A. H.-6 the excretion on the higher dose was found to be almost continuous after the first week. For R. N.-6 (a peculiar cycle in that no indication of estrin excretion was found at the usual dose) the higher dose showed that estrin was being excreted, although at a low level, for R. N.-7 the curves parallel each other.

Summarizing the data concerned with estrin excretion, a two-wave type of curve appears to be normal although the waves themselves are irregular in outline; at the peak some 600 to 800 I. U. are excreted daily; assay at high dosage shows estrin may be excreted throughout the cycle except for the first week.

A comparison of the time of occurrence of corresponding estrin and gonadotropin peaks leads to the interesting finding that the excretion of estrin invariably precedes that of gonadotropin. Presumably the same is true of their production by the glands involved, and, if this finding is verified, the somewhat unexpected conclusion must be reached that the original stimulation to ovulation is ovarian rather than hypophyseal in origin. While at variance with the commonly accepted view that the pituitary is the motor governing ovarian function, this finding is supported by the results of animal experimentation, which indicate

that the first effect of estrin upon the pituitary is to stimulate it to secrete (or release) gonadotropin. Briefly, the mechanism of ovulation may then be postulated as follows: The pituitary maintains the growth and development of the ovary continuously. This is evidenced by the effects of hypophysectomy primarily, plus the slight additional verification presented in the described assay for gonadotropin at high dosage levels. With the ripening of the follicle, the secretion of estrin begins, probably as early as the seventh day, increasing in amount until it builds up to a peak. This increasing concentration acts as a stimulus to the pituitary whose increased output is demonstrated by the appearance of the gonadotropin peak. That this gonadotropin is pituitary in origin seems likely[4] but whether it differs only in amount or perhaps qualitatively as well from the ovary-maintaining principle is not known. It is believed[5] that a proper combination of both follicle-stimulating and luteinizing hormones is necessary for ovulation; that addition of luteinizing hormones to follicle-stimulating hormone preparations gives an augmented ovarian reaction in the immature rat[6]; and there is evidence that the chief effect of estrin stimulation on the pituitary is, at first, to increase the output of luteinizing hormone.[7]

The second wave of estrin secretion, usually as great as or greater in amount than the first, does not usually result in a rise in gonadotropin. This estrin is presumably secreted by the corpus luteum and its inability to stimulate the pituitary must be due to the inhibiting effect of the progestin being produced simultaneously. To check this point, as well as to render the picture complete in other respects, simultaneous determination of progestin (pregnanediol) is necessary. We have attempted to do this by the method of Venning[8] but although satisfactory for pregnancy urine, we have not been able to convince ourselves of the reliability of this method as applied to daily samples of normal urine.

There remain to be considered the few cycles which do not fit into the theory suggested above. In the second cycle of L. W. (Chart 1), it appears that the estrin output, although apparently normal, did not result in sufficient hypophyseal stimulation to produce a peak. From the failure of a second estrin wave to appear, one might assume that ovulation had not occurred. Cycle R. N.-6 shows an apparent failure of estrin secretion, consequently no hypophyseal activity and no ovulation. Cycles M. S.-3 and A. H.-6 are anomalous and cannot be explained, as in both cases a second wave of estrin (presumably from the corpus luteum) occurred without the hypophyseal activity assumed to be necessary for ovulation. These occasional aberrant cycles cannot fail to cast doubt both on the validity of the theory and the reliability of the method. I can only repeat that, for the establishment of either, the accumulation of more data is an absolute necessity.

SUMMARY

Day-by-day assays, for both estrin and gonadotropin, during a total of 29 cycles, of 5 subjects, have been made. The results were as follows:

1. As regards time of ovulation: Of the 29 cycles, 25 gave evidence of ovulation occurring between the twelfth and sixteenth days preceding the onset of the next menstruation; the other 4 were considered anovulatory.

2. As regards hormone excretion levels: The amount of gonadotropin produced during peaks of activity was equivalent to from 4 to 16 I. U. Some evidence was obtained supporting the view of hypophyseal activity at other times than the mid-interval. The excretion of estrin took place in two waves, the daily output at the peak being approximately 800 I. U. Some degree of estrin excretion may take place at other times during the cycle except during the first week.

3. As regards time relationship of hormone excretion: Invariably the ovarian activity, as indicated by increasing estrin excretion, precedes hypophyseal activity, as indicated by the gonadotropin peak. On the basis of this finding a theory of the mechanism controlling ovulation is tentatively suggested.

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AN EVALUATION OF THE EFFECT OF ANTENATAL ANTISYPHILITIC THERAPY ON FETAL MORTALITY AND ON CONGENITAL SYPHILIS

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ONE of the greatest steps forward in the history of obstetrics was the advent of the treatment of syphilis in the pregnant woman,[1] with the coincident reduction of fetal death rate and incidence of fetal infection. Prior to this time not only one-half of the fetuses of these women were born dead but also only a small number of those both dead and living were found to be unaffected by the virus.[2-5] With institution of adequate treatment the reduction of this astounding devastation of fetal life has been almost miraculous, and striking results have been obtained even with scanty amounts of therapy.[6-9]

There is no room for doubt that adequate antisyphilitic therapy instituted early in the course of pregnancy will greatly reduce the number of disastrous and infected products of conception, and studies have shown that therapy prior to conception, even inadequate, materially affects the incidence of infection in the fetus.[8, 10, 11]

Although we have seen a comparatively large number of pregnant women with positive serology, we have been impressed with the scarcity of signs and symptoms of congenital syphilis in the fetuses and with

the relatively few babies found to be syphilitic in the pediatric follow-up clinic. This impression becomes even more significant when one takes into account the incidence of patients seen late in pregnancy and the number in whom irregular and inadequate therapy had been instituted.

Much has been written recently concerning the reaction of the pregnant woman to the arsenicals[9, 12, 13] and of the beneficial effect of pregnancy on the syphilitic state.[14] Very little is known concerning the effect of these drugs on the fetus in utero although some believe that antisyphilitic therapy probably does carry a mortality rate for the fetus.

Because of the occasional occurrence of definitely syphilitic babies from mothers showing no clinical signs of the disease and whose serology is negative, many obstetricians have adopted the rule of treating every patient during pregnancy whose serology is suggestive or whose history or that of her husband gives positive evidence of this disease or of treatment for it.[11] It seems obvious that such rules bring under this regimen those patients who have been thoroughly treated and biologically cured of syphilis as well as a few patients who have never had the disease.

The records of the patients who have been treated in this Hospital for the past seven years have been examined in an effort to obtain a clearer view of the factors which play a part in the satisfactory outcome of the fetus; to determine, if possible, which patients may expect a satisfactory outcome of the pregnancy; and to attempt to find whether type and amount of antisyphilitic therapy as such appreciably affect the fetal mortality and incidence of infection.

MATERIALS AND METHODS

The charts of 386 patients in whom 453 pregnancies had occurred were reviewed. One hundred ninety-two of these pregnant women had been delivered on the in-patient service of the New York Lying-in Hospital and 261 had been cared for on the out-patient service of this hospital at the John E. Berwind Free Maternity Clinic of New York City.

All of these patients had had pregnancies occurring between the years 1932 and 1939, inclusive, and had been registered in these services. All had received routine antenatal care in addition to the antisyphilitic therapy, and each patient had been given more than one treatment for the suspected syphilis.

The scale of society from which these people came ranged from the very poor, most of which were Berwind Out-door Clinic patients, to the middle stratum of society seen in the New York Hospital. Two hundred and thirty-nine of these pregnancies were in colored and 214 in white women.

Upon registration the prospective mothers had been subjected to a thorough medical history and a complete physical examination. Laboratory work on all patients consisted of a serologic test for syphilis (Wassermann or Kline) and a hemoglobin determination of the blood; albumin and sugar were tested for in the urine.

Following the finding of a history of syphilis, a history of treatment, or positive or questionable serology, the patient was immediately referred to the syphilitic clinic where a more complete venereal history was obtained and the serology repeated with specimens being sent to the Laboratories of the Board of Health of the City of New York. In doubtful cases the families of the patients were investigated. All patients were treated during the pregnancy who had histories of syphilitic infection, who had been treated previously for this disease, or whose serology and family investigation failed to leave any reasonable doubt that the patient might have syphilis.

The treatment at the in-patient department has consisted for the most part of continuous therapy with arsphenamine alternated with courses of bismuth. Some of the patients have received neoarsphenamine and bismuth in alternating courses and some have received them in combined therapy. Recently combined therapy with mapharsen and bismuth has been instituted. A few patients have had indications for the use of tryparsamide or silver arsphenamine, but these have been infrequent. At the Berwind Clinic all therapy consisted of neoarsphenamine, alternated with courses of bismuth.

At the time of delivery, the maternal and cord Wassermanns were done, and the placenta examined grossly and microscopically. The blood Wassermann reaction of the baby and x-rays of the long bones were done six to nine days post partum.

Autopsies were obtained on all but a few of the dead babies and spirochetes were routinely searched for in most of these bodies. A culture of the heart blood was usually done.

All living babies were routinely referred to the pediatrics department of the hospital for follow-up observations and were seen at three-month intervals or more frequently if conditions warranted. The babies from the Berwind Clinic were referred usually to this clinic or to the nearest City health center. Routine serologic tests, x-ray studies of the long bones, and careful physical examinations were made at regular intervals. An attempt was made to follow all babies for eighteen months if proved to be not infected, and for a longer period if syphilitic.

The charts of these patients were studied from the points of view of the age, race, and outcome of the previous pregnancies. The blood Wassermanns on admission, at delivery, and at six weeks and two years post partum were recorded as well as the duration of antenatal care and duration of the pregnancy. The labor was studied with reference to duration, type of pelvis, and complications of the normal mechanism in order to rule out obstetric trauma as a cause of death or poor condition of the baby. The baby was studied as to condition at birth, length, weight, x-ray of long bones, cord Wassermann, placental weight and pathology. The condition of the baby and the blood Wassermann at six weeks and at the end of the pediatric follow-up were also considered.

The previous course of the mother, when known, with reference to the serology, duration of the disease, and exact amount of previous treatment, was recorded. (Records from the source of treatment were consulted when possible; otherwise the history of the patient was taken as the source.)

The treatment during the present pregnancy was recorded as to duration, amount and type, and severe treatment reactions were noted. The course following delivery at the end of six weeks and two years with the serology and type of treatment was included.

In the classification of babies of the series observed, babies were considered "term" which were above 2,500 Gm. in weight or above 45 cm. in length. Babies were considered premature which weighed from 1,500 to 2,500 Gm. or were below 45 cm. in length. All products of conception from 100 to 1,500 Gm. were considered "late abortions" and those below 100 Gm. were considered "early abortions."

The classification of babies of the previous pregnancies was carried out as follows: Babies were considered "term" which were above 5 pounds or later than eight months; babies were considered premature which were above 3 pounds or later than seven months' gestation; when delivery occurred between the fourth and sixth months the product was considered to be a "late abortion" and when prior to the fourth month was considered an "early abortion."

Babies were classified as normal only after numerous physical examinations, blood serologies and x-rays of the long bones over a period of six months or more had failed to reveal evidence of the disease. No babies were classified as syphilitic by autopsy since none were found to have spirochete-containing tissue.

Under the classification of abortions no pregnancies terminated by induction or operative interference were included in this series, either in the previous or the present pregnancies.

The two groups are not quite comparable in that any serious complication of the antenatal course or delivery encountered at Berwind Clinic is referred to the New

York Hospital or rarely to one of the New York City hospitals. No patients are included in this series who were not delivered at Berwind or in the New York Hospital, although a few of the Berwind cases were lost to City Hospitals because of complications. In this sense the New York Hospital series and the Berwind series are complementary rather than comparable.

CONTROLS

Four hundred and fourteen patients who had 500 pregnancies, 200 pregnancies from the New York Hospital and 300 from the Berwind Clinic, were used as controls for the syphilitic series. Approximately an equal number of consecutive deliveries were taken from each of the years included in the syphilitic group. These patients were taken care of in the same manner as the syphilitic group, but at no time showed evidence of even doubtful serology and had no history of syphilitic infection or treatment for this disease. An effort was made to approximate the parity and the age of the patients in the syphilitic group (Table I). It is to be noted, however, that the percentage of colored patients in the control group is considerably lower than the percentage in the syphilitic series. No follow-up observations on these babies are available and no Wassermann test or long bone studies were made, except of stillborn babies.

No effort was made to collect a series of untreated syphilitic patients, as the paucity of the material would make these figures statistically unsound.

TABLE I. COMPARATIVE DATA ON THE OBSTETRIC TYPE OF PATIENT INCLUDED IN THIS SERIES

	SYPHILITIC		CONTROL	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Number of patients	175	211	142	272
Race {White	115	81	128	171
Race {Colored	60	130	14	101
Average age	27.7	29.5	27.3	28.8
Number of previous pregnancies	349	831	238	876
Average per patient	1.9	3.8	1.6	3.2
Number of pregnancies observed	192	261	200	300
Babies followed	149	73	---	---
*Maternal serology {Positive	142 (74%)	----	---	---
*Maternal serology {Negative	50 (26%)	----	---	---
†Maternal Wassermann {Positive	121 (63%)	198 (76%)	0 (0%)	0 (0%)
†Maternal Wassermann {Negative	71 (37%)	63 (24%)	200 (100%)	300 (100%)

*Both Wassermann and Kline tests were done on N. Y. Hospital patients.
†Only the Wassermann test was done on the Berwind group.

OUTCOME OF PREVIOUS PREGNANCIES

The 386 patients of our syphilitic series had had 1160 previous pregnancies, almost two each for the New York Hospital group and four each for the Berwind group (Table II). Although the Berwind group showed slightly more living term pregnancies than the New York Hospital group, more than two-thirds of these pregnancies in each group had ended in term deliveries and had resulted in living children, which at this time are living and clinically well or have succumbed to one of the usual childhood diseases, according to the maternal history. The nonsyphilitic controls show a similar group difference although a distinctly higher percentage of term living fetuses is noted.

The greatest loss of life in both syphilitic and control group occurred in the early abortion division, with a noticeably higher incidence in the New York Hospital series.

The number of term deadbirths and neonatal deaths as well as premature deadbirths and late abortions was significantly higher in the syphilitic groups than in the nonsyphilitic control groups.

TABLE II. SHOWING THE OUTCOME OF PREVIOUS PREGNANCIES IN THE TWO GROUPS OF SYPHILITIC PATIENTS AS COMPARED WITH SIMILAR PREGNANCIES IN ANALOGOUS GROUPS OF NONSYPHILITIC MOTHERS

		SYPHILITIC		CONTROL	
		N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Number of patients		175	211	142	272
Total pregnancies		343	817	238	876
Term	Living	233 (67.9%)	614 (75.2%)	190 (79.8%)	751 (85.7%)
	Deadborn	14 (4.1%)	38 (4.7%)	5 (2.1%)	13 (1.5%)
	Neonatal	7 (2.0%)	18 (2.2%)	0 (0.0%)	8 (0.9%)
Premature	Living	2 (0.6%)	8 (1.0%)	1 (0.4%)	3 (0.3%)
	Deadborn	7 (2.0%)	38 (4.7%)	2 (0.8%)	0 (0.0%)
	Neonatal	1 (0.3%)	5 (0.6%)	2 (0.8%)	4 (0.5%)
Abortions	Early	65 (18.9%)	68 (8.3%)	35 (14.7%)	91 (10.4%)
	Late	14 (4.1%)	28 (3.4%)	3 (1.3%)	6 (0.7%)

OUTCOME OF PRESENT PREGNANCIES

More than 80 per cent of the pregnancies of syphilitic patients in the New York Hospital group and 90 per cent of the Berwind pregnancies observed terminated in living term babies, a percentage which is significantly lower than the corresponding number occurring in the nonsyphilitic control patients (Table III).

In these pregnancies the greatest loss of life occurred in the term deadbirth and neonatal death groups, this loss exceeding the control figures by more than 100 per cent. Here again there is a considerable preponderance of fetal mortality in the New York Hospital group.

The number of premature living babies and premature neonatal deaths is distinctly increased over control levels only in the New York Hospital cases.

The high incidence of early abortion of the New York Hospital control group is well out of proportion to both syphilitic groups and to that seen in the Berwind nonsyphilitic patients.

TABLE III. SHOWING THE OUTCOME OF PRESENT PREGNANCIES WITH TREATMENT IN SYPHILITIC PATIENTS AS COMPARED WITH SIMILAR PREGNANCIES IN ANALOGOUS GROUPS OF NONSYPHILITIC MOTHERS

		SYPHILITIC		CONTROL	
		N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Number of pregnancies		192	261	200	300
Term	Living	148 (77.1%)	239 (91.6%)	172 (86.0%)	289 (96.3%)
	Deadborn	14 (7.3%)	6 (2.3%)	6 (3.0%)	2 (0.7%)
	Neonatal	8 (4.2%)	7 (2.7%)	1 (0.5%)	1 (0.3%)
Premature	Living	12 (6.3%)	4 (1.5%)	6 (3.0%)	4 (1.3%)
	Deadborn	1 (0.5%)	2 (0.8%)	1 (0.5%)	2 (0.7%)
	Neonatal	4 (2.1%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Abortions	Early	2 (1.0%)	1 (0.4%)	10 (5.0%)	0 (0.0%)
	Late	3 (1.6%)	1 (0.4%)	4 (2.0%)	2 (0.7%)

EVALUATION OF DIAGNOSTIC CRITERIA FOR CONGENITAL SYPHILIS

With pediatric follow-up of more than 6 months we were able to find only 9 pregnancies resulting in babies which could definitely be called syphilitic, and all of these were subjected to treatment (Table VIII). Two other babies, subjected

to treatment before the end of the first month of life, had an immediate reversal of serology. Therapy was discontinued after a few months and long follow-up failed to reveal return of the positive serology or clinical evidence of syphilis; therefore these babies were considered normal.

It is obvious that the percentage of syphilitic babies is higher in the group where the maternal Wassermann was positive, but we were unable to find any significant difference in the number of fetal casualties.

It is of interest to note that we found 4 infants in whom the blood Wassermann failed to become negative even after two or three months, and in one case it remained positive for six months. These children have shown no clinical evidence of syphilis and with no treatment have remained clinically and serologically free from the disease for more than four years.

TABLE IV. SHOWING THE INCIDENCE OF SIGNIFICANT CHANGES IN THE PLACENTA AND THE LONG BONES OF THE INFANT AND OF A POSITIVE REACTION OF THE CORD BLOOD AND OF THE MOTHER'S BLOOD TO THE STATUS OF THE FETUS

		SYPHILITIC BABIES		NONSYPHILITIC BABIES	
		N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Number of babies followed		9	0	131	68
Cord Wassermann	Negative	1 (11%)	0 (0.0%)	86 (81%)	49 (83%)
	Positive	8 (89%)	0 (0.0%)	20 (19%)	10 (17%)
Placenta	Negative	8 (100%)	0 (0.0%)	97 (98%)	40 (91%)
	Positive	0 (0.0%)	0 (0.0%)	2 (2%)	4 (9%)
Long bones	Negative	7 (78%)	0 (0.0%)	81 (96%)	42 (98%)
	Positive	2 (22%)	0 (0.0%)	3 (4%)	1 (2%)
Maternal Wassermann	Negative	1 (11%)	0 (0.0%)	50 (38%)	14 (21%)
	Positive	8 (89%)	0 (0.0%)	81 (72%)	54 (79%)

We were surprised to find that roentgenograms of the long bones were frequently in error in the diagnosis of congenital syphilis on the appearance of the irregularities of the bone metaphysis. Approximately 95 per cent of the x-rays of the long bones were negative for syphilis when the baby was normal, but 2 to 4 per cent of these babies also showed the changes which were diagnosed as definitely syphilitic by McLean's criteria.[15-17] Of the syphilitic babies, 20 per cent were found to have bone changes compatible with congenital syphilis, but in 80 per cent the bones were considered negative for significant x-ray changes (Table IV).

Placental findings were also of note in that 90 to 95 per cent of the placentas from the nonsyphilitic children were classified as normal, while 2 to 4 per cent of these babies had placentas which were classified as syphilitic according to the changes described by Frankel.[18] In the syphilitic group, none of the placentas showed histologic evidence of syphilis.

Of the cord Wassermanns done on 6 of the syphilitic babies, only one was found to be negative, and here the Kline test was strongly positive. The cord Wassermann was positive in 16 to 18 per cent of the normal babies and negative in 80 to 85 per cent. We found only one positive cord Wassermann in a mother whose blood Wassermann was reported repeatedly negative and this baby was definitely syphilitic. It is worthy of note, however, that the Kline reaction in this patient was strongly positive.

No babies either deadborn or dying in the neonatal period were found to be syphilitic at post-mortem examination, either by the supposedly characteristic changes in the bones or by finding spirochetes in the tissues.

The placental weights and the weights of the babies of syphilitic mothers of both groups were compared with those of the control groups (Table V). The Berwind babies averaged about 100 Gm. more than those of the New York Hospital group, and the controls were slightly heavier than the babies of the syphilitic mothers.

TABLE V. SHOWING THE AVERAGE PLACENTAL WEIGHT AND AVERAGE BABY WEIGHT IN THE TWO GROUPS OF SYPHILITIC PATIENTS AS COMPARED WITH THE TWO ANALOGOUS GROUPS OF NONSYPHILITIC PATIENTS. SIMILAR AVERAGES ARE ALSO SHOWN FOR THE SYPHILITIC BABIES

	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
All babies:				
Average placental weight	636.1	616.5	648.7	611.0
Average baby weight	3223.4	3460.8	3312.2	3549.5
Syphilitic babies:				
Average placental weight	640.0	----	----	----
Average baby weight	3234.0	----	----	----

The placental weights were not consistently different.

The weights of the babies and of the placentas of the group of babies found later to be syphilitic were not significantly different from the remainder of the group.

EFFECT OF TREATMENT

Because of the size of the series and the relatively small number of syphilitic babies found, it is impossible for us to attempt to determine the effects of treatment except in relation to the number of syphilitic babies and the number of fetal deaths occurring in the different treatment groups and the different age groups.

A steadily progressive diminution of syphilitic babies is noted with the increased amount of therapy that the mother received antepartum and only one fetus was found to be syphilitic whose mother received more than 6 grams of an arsenical preparation (Chart 1).

No correlation of total amount of bismuth therapy to the evidence of syphilitic infection of the fetus was noted (Chart 2).

The occurrence of deadborn babies and neonatal fetal deaths was not found to vary directly with the amount of either type of treatment received. On the contrary, with advancing dosages of both arsenic and bismuth, there was found to be a steady fall in the number of fetal casualties until, with good therapeutic doses of arsenic, a number not exceeding the control level was obtained.

The effect of treatment prior to the pregnancy is of considerable interest and importance (Table VI).

It is worthy of note that no syphilitic babies were obtained in the group receiving treatment both prior to and with the pregnancy, even though a considerable number of these patients received minimal treatment in both instances.

An attempt to correlate the number of dead babies with the presence of previous treatment showed a noticeably lower incidence, seemingly within control levels, for this group, while those receiving no treatment prior to the pregnancy had a noticeably higher fetal mortality rate.

We were unable to correlate the amount of previous treatment with the number of fetal deaths and could find no effect of previous treatment on the fetal mortality of the previous pregnancies.

The time of onset of treatment in the pregnancy was correlated with the incidence of syphilitic and dead babies. The incidence of syphilitic babies was found to decrease significantly as the length of treatment increased. More fetal deaths, however, occurred in patients registering early, although the peak of fetal death was noted later in the control group and fell below the syphilitic group approaching term (Chart 3).

INFLUENCE OF THE AGE OF THE PATIENT

We attempted to correlate the incidence of dead and syphilitic babies with the age of the infection, using the age of the patient as a rough index of the duration of the infection in the mother. It seemed quite obvious that the higher

percentages of syphilitic babies were noted in the younger age groups, and that the incidence of infected babies dropped off with the ascending age of the patient. This was also found to be true for the percentage of dead babies, with the single exception of those occurring in the "40 years of age" group. We were not, however, able to show that the increased age placed the patient in a safe class for prognosis for the fetus inasmuch as syphilitic babies were observed even in the older age groups (Chart 4).

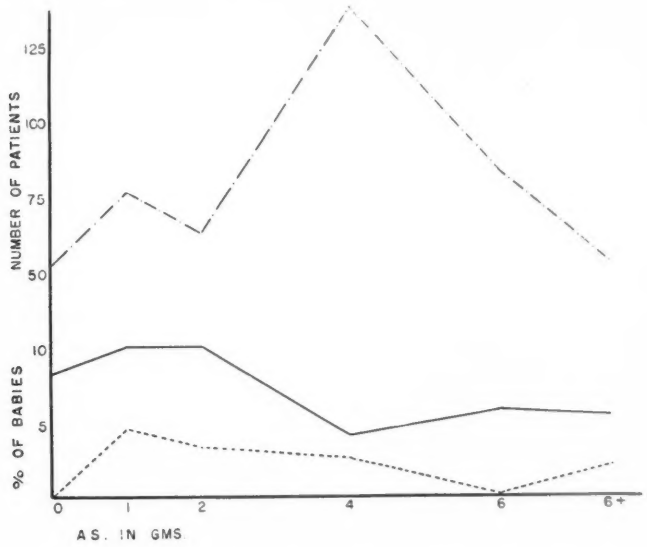

Chart 1.—The distribution of patients, infected fetuses, and fetal mortality with regard to the amount of arsenical therapy received by the mother during the antenatal course. —.—., Number of patients; ———, per cent of dead babies; - - - - -, per cent of syphilitic babies.

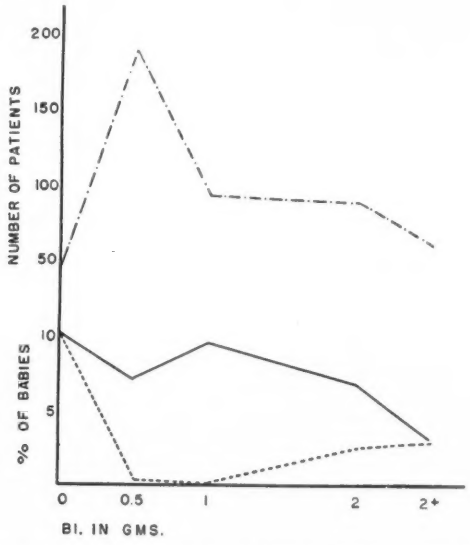

Chart 2.—The distribution of patients, infected fetuses, and fetal mortality with regard to the amount of bismuth therapy received by the mother during the antenatal course. —.—., Number of patients; ———, per cent of dead babies; - - - - -, per cent of syphilitic babies.

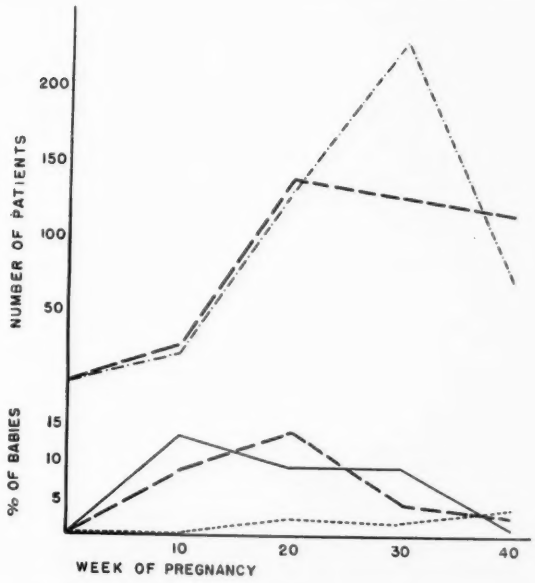

Chart 3.—The distribution of syphilitic and control patients, infected fetuses, and fetal mortality in both the syphilitic and control groups with regard to the week of pregnancy in which registration occurred or in which treatment was started. —.—., Number of syphilitic patients; — — —, number of control patients; - - - - -, per cent of syphilitic babies; ————, per cent of dead babies in the syphilitic group; — — —, per cent of dead babies in the control group.

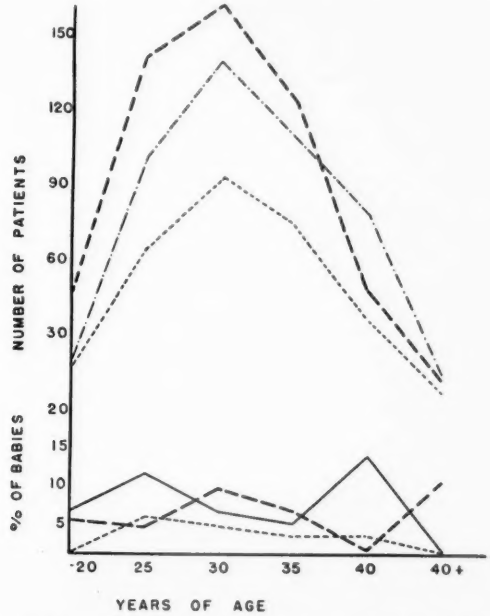

Chart 4.—The distribution of syphilitic and control patients, infected fetuses, and fetal mortality in both syphilitic and control groups with regard to the age of the mother at the time of delivery. —.—., Number of syphilitic patients; - - - - -, number of syphilitic patients whose babies were followed in pediatrics; — — —, number of control patients; - - - - - -, per cent of syphilitic babies; ————, per cent of dead babies in the syphilitic group; — — —, per cent of dead babies in the control group.

TABLE VI. SHOWING THE EFFECT OF PREVIOUS TREATMENT ON THE OUTCOME OF PREGNANCY

	SYPHILITIC PATIENTS		CONTROLS
	WITH PREVIOUS TREATMENT	WITH NO PREVIOUS TREATMENT	
Number of pregnancies	260	193	500
Babies followed	123	88	---
Syphilitic babies	0 (0.0%)	9 (10.2%)	---
Dead babies	17 (6.5%)	16 (8.4%)	29 (5.8%)

COMPLICATIONS OF PREGNANCY

Dystocia, pyelitis, and ante-partum bleeding were not noted to have an increased frequency in either syphilitic group. Three patients delivered hydatidiform moles, an incidence of 0.66 per cent of the total group. Toxemia of pregnancy, however, was found to have a real increase in incidence, although this increase could not be correlated with the amount of treatment nor with the time it was begun, nor with the amounts of arsenic or bismuth received (Table VII). It would seem that the lower incidence in the Berwind syphilitic group as compared with the controls in that clinic merely means that a greater percentage of these patients had been sent to the New York Hospital.

TABLE VII. SHOWING THE INCIDENCE OF TOXEMIA IN SYPHILITIC AND CONTROL GROUPS

	SYPHILITIC		CONTROL	
	N. Y. HOSPITAL	BERWIND	N. Y. HOSPITAL	BERWIND
Total pregnancies	192	261	200	300
Cases with toxemia	29	8	15	14
Per cent with toxemia	15.1	3.1	7.5	4.7

DISCUSSION

The incidence of dead and syphilitic babies in this series is very small and well bears out the clinical impression that syphilis need be no longer the primary cause of death in the fetus nor a frequent disease in the newborn.

McCord[19] has shown that the previous pregnancies which occurred in his series of patients had resulted in large numbers of disastrous terminations, and untreated syphilitic patients have been shown[8] to have a comparably high fetal mortality rate. The group of pregnancies in our previously untreated patients showed 65 to 75 per cent living babies and no significant difference could be made out when compared with previous pregnancies of the group which had been treated sometime previously.

The outcome of the present pregnancies corresponds well with figures previously reported for treated series.[7-9] Although the incidence of stillbirths is slightly higher than that in a similar group of control patients, this difference is not alarming, and the low incidence of infected babies is most gratifying.

One explanation for this lowered mortality and incidence of fetal infection is obviously antenatal therapy. The treatment received prior

to pregnancy certainly plays a fundamental part. The fact that a large number of patients who had received minimal amounts of treatment during the pregnancy, prior to it, or both, and still had a satisfactory outcome suggests that a fair number of these patients had received their infection very early in life, and that it had become attenuated with the passage of time prior to conception.[11] It is also possible that the disease itself has become less virulent since the advent of modern therapeutic methods.

The only method we have considered as absolute in the diagnosis of syphilis in the fetus is a pediatric follow-up of six months or more, and to this have been compared other generally used methods. Although this period of time is probably not sufficient to be absolute, it is felt that the small number of babies who might develop positive serology or clinical symptoms and signs following this time would not materially alter our statistics.[20]

An attempt to follow all babies from eighteen months to two years was made and failure to report for clinic appointments was vigorously investigated by the Social Service Department. Loss of cases in the follow-up was more evident in the non-syphilitic group than in the syphilitic group since more effort was made to follow the baby where doubt was felt for the syphilitic status than where the nonsyphilitic status was considered relatively certain.

The findings of the x-ray of the long bones, placental histology, and cord Wassermann bear out this faith in the pediatric follow-up and the real lack of specificity of any or all of the other means of diagnosis.

The relative value of the x-ray diagnosis is of course colored by individual interpretation of the films; and antisyphilitic and other types of medication (particularly bismuth), varying bone densities and poor plates all probably decrease their reliability. Numerous types of bone abnormalities have been shown to be confused with the type of lesions produced by syphilis.[15-17, 21]

Although placental histology as a diagnostic aid to congenital syphilis has been time honored,[18] it has not been generally recognized that the typical picture was originally applied only to macerated fetuses.[22] Here again individual interpretation plays a great part in the diagnosis.[23-25] It also seems obvious that extraneous factors such as prematurity and vascular diseases of the placenta which are nonsyphilitic in origin may serve to produce the same picture.

The cord Wassermann seems to be of value as an absolute diagnostic aid in congenital syphilis only when it is positive and the maternal blood Wassermann is negative. It is recognized, however, that a fetus born with a negative cord Wassermann may develop syphilis.

Although this series and those previously reported bear out the fact that the x-ray of the long bones, placental histology, and cord Wassermann more often show the so-called pathognomonic changes when the baby is syphilitic,[7-9] it is also significant that none of the criteria are absolute. Also the baby may be syphilitic but show none of these signs.

TABLE VIII. GIVING PERTINENT DATA ON BABIES FOUND TO BE SYPHILITIC THROUGH PEDIATRIC FOLLOW-UP

MOTHER						BABY						MOTHER'S TREATMENT				
CASE	RACE	AGE	PARITY	DIAGNOSIS	WASSERMANN	CONDITION AT BIRTH	CORD WASSERMANN	X-RAY OF LONG BONES	PLACENTAL PATHOLOGY	DIAGNOSTIC CRITERION	PEDIATRIC FOLLOW-UP	PRIOR TO PREGNANCY	DRUG	AMOUNT	DURATION OF OBSERVATION IN WEEKS	COMMENT
13	White	24	ii	Latent	4+	Living Term	4+	Suggestive	Neg.	Clin.	1½ yr.	0	Neo. Bi.	3.6 2.3	19	Baby: Lymph nodes and spleen palpable. X-ray showed periostitis for 6 wk. Wass. 6 wk. +; neg. with treatment 1½ yr. Mother: No lapse in treatment during this pregnancy. First pregnancy resulted in mole and abortion. Wass.: 6 wk. +; neg. with treatment 1½ yr.
76	White	24	ii	Latent	Wass. neg. Kline 4+	Living Term	4+	Neg.	Neg.	Clin.	2 yr.	0	As.	1.7	16	Baby: Snuffles. Wass.: 6 wk. 4+; neg. with treatment 2 yr. Mother: No lapse in treatment during this pregnancy. First baby died at 3 months of "cold." Wass.: 6 wk. neg.; treatment for 3 yr. following.
96	White	23	i	Latent	4+	Living Term	Wass. neg. Kline 4+	Suggestive	——	Clin.	3 yr.	0	Neo. As.	1.6 0.6	8	Baby: Questionably syphilitic. X-ray showed periostitis. Wass.: neg. 6 wk. and 2 yr. Kline 4+ even 4 yr. later. Mother: No lapse in treatment during this pregnancy. Wass.: 6 wk. 2+; neg. with treatment 2 yr.
97	Col.	31	i	Latent	4+	Living Term	—	Syphilitic	——	Clin.	3 yr.	0	As. Bi.	2.2 1.6	30	Baby: Questionably syphilitic. Bones showed thickening of the periosteum for 7 months. Wass.: neg. 6 wk. and 2 yr. Mother: Lapse in treatment for last 1½ months of this pregnancy. Wass.: neg. 6 wk. and 2 yr. Treatment 4 months following.

104	White	28	i	Latent	3+	Living Term	—	Neg.	Neg.	Clin.	½ yr.	0	As.	1.3	9	Baby: Definitely syphilitic. Wass.: neg. 6 wk.; 6 months 4+. Not followed after 6 months. Mother: No lapse in treatment during this pregnancy.
127	White	39	viii	Late latent	4+	Living Term	4+	Neg.	Neg.	Clin.	2 yr.	0	Neo. Bi.	0.6 0.4	20	Baby: Long bones showed increased density adjacent to the epiphysis at 3 yr. Wass.: 6 wk. 4+; 2 yr. neg. Treatment 1½ yr. Mother: Lapse in treatment for last 1½ months of this pregnancy. Three spontaneous abortions at 8 wk. Wass.: 6 wk. and 2 yr. 4+. Treatment 3 yr. following.
140	Col.	29	i	Latent	4+	Living Term Twins	A. 4+ B. —	Neg. Neg.	Neg. Neg.	Clin. Clin.	2 yr. 2 yr.	0	As. Bi.	1.8 1.6	15	Babies: Wass.: 6 wk. 4+; 2 yr. neg. Treatment 1½ yr. Mother: Lapse in treatment for 5 months in the middle half of pregnancy. Wass.: 6 wk. and 2 yr. 4+. Treatment 3 yr. (Wassermann fast.)
146	White	31	iii	Latent	4+	Living Term	4+	Neg.	Neg.	Clin.	2 yr.	0	Neo. As.	0.3 0.6	7	Baby: Wass.: 6 wk. 4+; neg. 2 yr. Treatment 1½ yr. Mother: No lapse in treatment during this pregnancy. Wass.: 6 wk. 4+; 2 yr. 3+. Treatment 4 yr. Still being treated.
183	White	32	iv	Early latent	3+	Living	—	Pos.	Neg.	Clin.	1 yr.	0	As. Bi.	7.05 3.2	12	Baby: Petechiae of skin; desquamation of soles of feet and palms of hands; secondary syphilis diagnosed at birth. Wass.: 4 wk. 4+; neg. at 6 wk. following beginning of treatment. Spleen palpable. Long bones showed lines of linear density at the metatarsals suggesting treated prenatal syphilis. Treatment 1 yr. Mother: No lapse in treatment during this pregnancy. Wass.: 6 wk. and 1 yr. 4+. Treatment 1 yr. Still being treated.

It has also been noted that the reagin titer of the baby's blood may remain high for much longer periods of time than have been generally accepted,[26] while the fetus may still fail to show signs of syphilis after prolonged follow-up. These observations tend to suggest that syphilis should be neither diagnosed nor treated until sufficient observation has been carried out.

This series confirms the previous work that a patient who receives more than 4 Gm. of arsenic has less than a 5 per cent chance of bearing a syphilitic child.[9] Even more than 6 Gm. during the antenatal course, however, do not absolutely insure a nonsyphilitic fetus.[10]

The reduction in fetal mortality and infection associated with the early onset of treatment is quite evident in this series as in the previously reported patients.[8-10]

Treatment received both prior to and during pregnancy produces the most striking and reliable effect on fetal incidence of infection and mortality. Although this finding has been previously described,[8, 10] its real significance has not been appreciated by many physicians treating pregnant women. Among these patients of our series, no syphilitic infections were noted and the fetal mortality was comparable to that of the nonsyphilitic, nontreated controls.

One of the original purposes of this study was to determine what effect treatment alone played in the production of fetal mortality. In taking that group in which the incidence of syphilitic infection of the fetus is at a very low figure (patients who had received treatment prior to and during this pregnancy), we find that the mortality rate is quite comparable to that of a similar group of normal, nonsyphilitic patients in whom no treatment has been carried out. This is also borne out by the low mortality rate of fetuses whose mothers have received early and adequate treatment.

The high incidence of fetal mortality and fetal syphilitic infection in the group receiving minimal amounts of therapy suggests that this mortality is due to syphilitic infection of the fetus. This would also tend to show that if antisyphilitic therapy causes fetal death (which we cannot demonstrate), it occurs as in the adult as a sensitivity reaction in the early course of treatment, and therefore no real advantage would be obtained by giving the suspected mother a few treatments for prophylaxis of the child.

It is known that the patients with old infections have less tendency to transmit the disease to the fetus,[11] and our figures, using the age of the patient as an index to the duration of infection, tend to substantiate this finding. However, since most of these patients have no knowledge of the duration of the infection, it is unsafe to use age as a basis for giving or withholding treatment.

There seems to be a significant rise in fetal mortality in the earlier age groups, and also in the elderly patients. Cole[9] has postulated that the early rise is due to the activity of a recent infection, and the rise of fetal mortality late in life is similar to that described in control patients

by Sterling.[27] Our control figures do not bear out either rise, but it seems likely that our figures in both the very young and the very old groups may not be significant, due to the small number of patients.

We are unable to explain why the toxemias of pregnancy occur more frequently in the syphilitic than in the nonsyphilitic patients. It is perhaps significant that 70 to 80 per cent of the toxemic patients had positive Wassermans but previous treatment or the amount and type received during the present pregnancy could not be correlated with the incidence of toxemia.

The incidence of hydatidiform mole was higher in this group of syphilitic patients than in the clinic as a whole.

CONCLUSIONS

Syphilis need no longer constitute a major cause of fetal mortality or a frequent disease of the newborn.

Antenatal therapy, which is responsible for the greater part of this effect, is greatly enhanced by treatment received prior to conception.

A favorable outcome is made more certain by early institution of treatment, advanced age of the infection, and negative serology.

No definite fetal mortality rate could be associated with adequate antenatal therapy.

The only satisfactory and reliable criterion of congenital syphilis in the infant is repeated clinical, serologic, and radiologic examination for a period of months or years following delivery.

The incidence of toxemia of pregnancy and of hydatidiform mole is definitely elevated in the syphilitic patient.

The authors wish to take this opportunity to thank Miss Gertrude Skelley, R.N. who has been largely responsible for making available reliable records on those patients seen at the John E. Berwind Free Maternity Clinic and to Dr. William L. Fleming, University of North Carolina School of Public Health, Chapel Hill, North Carolina, for aid and suggestions which have been invaluable.

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PSYCHIATRIC CONTRAINDICATIONS IN THE USE OF ESTROGENS DURING THE MENOPAUSE

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THE therapeutic management of the nervous menopausal female offers a challenging problem. Novak[1] has warned the physician not to be hasty in blaming a woman's climacteric experience for any peculiar symptom complex that defies usual diagnostic methods. After satisfactorily ruling out possible organic factors, attention may then be directed toward the menopause and its attendant ovarian insufficiency.

Investigators have demonstrated the efficacy of natural hormone substitutive therapy in cases of menopausal endocrine imbalance, but it should be noted that such reports emphasize that the beneficial effects are greatest in cases presenting *vasomotor* signs and symptoms. Werner[2] has written that the most frequent features of menopausal aggravation are: "excitability, irritability, headache, occipitocervical pain, crying, decreased memory and concentration, depression psychosis, and formication." These, with insomnia, are grouped by him under *nervous* manifestations. He lists the *circulatory* complaints in this order: "hot flushes, tachycardia, palpitation, dyspnea, vertigo, scotomata, cold hands and feet, numbness and tingling." These two categories, together with alterations in the established menstrual pattern, constitute the menopausal syndrome.

In determining a particular therapy for the menopausal patient, such listings as the above deserve close scrutiny. In middle-aged women, as these nervous symptoms are encountered, considerable variation is noted, both as to intensity and the subjective attitude of the patient toward them. A great deal of the irritability, depression, etc., is contingent upon the presence of hot flushes and other bizarre somatic sensations. Hence, the physician, whatever may be his specialty, is likely to be confronted by a few patients whose emotional balance has been notably affected by their distress over their hot flushes and other neurocirculatory symptoms. Novak states that only a small minority of menopausal females suffer notably from vasomotor complaints.[1]

In such a group as the latter, the careful use of any legitimate estrogenic preparation which has been demonstrated to abolish or minimize vasomotor symptoms is good treatment. And, so far as the patient's exaggerated emotional response is related to these vasomotor phenomena, the estrogens may be expected to aid the patient in regaining her psychic equilibrium. The doctor will aid her by such prescription with greater success provided her psychic turmoil is circumstantial rather than definitely systematized. Papanicolaou and Shorr[3] have called attention to this likelihood in their work on the action of ovarian follicular hormone in the menopause. Studying the patient's response

to estrogen by means of periodic vaginal smears, they "repeatedly found severely psychoneurotic patients highly resistant to treatment both as regards smear changes and symptomatic relief." The authors felt that this indicated some relationship between the menopausal syndrome and the psychic states noted during the climacteric.

Psychiatrists occasionally find it difficult to distinguish between the involved psychoneurotic and the actual psychotic patient. The menopause experience is capable of precipitating a profound mental disorder (psychosis): *involutional melancholia.* This type of mental aberration has been estimated as comprising from 3 to 4 per cent of all mental disease. Psychoses of other varieties are known to have their incidence in the climacteric era. Psychiatrists have long differentiated organic, affective (emotional; "benign") and schizophrenic (trend; "malignant") illnesses. Involutional psychoses, either the melancholic or paranoid types, fall into the affective grouping, as do the manic-depressive disturbances.

In 1897 Kraepelin called attention to the syndrome of involutional melancholia and regarded it as distinct from the other great affective class of manic-depressive disorders. However, he later signified agreement with his pupil, Dreyfus, when the latter, in 1907, returned the involutional syndrome to the manic-depressive category. Shortly thereafter, in a masterful evaluation of Dreyfus' work, Kirby[4] re-established the syndrome as a distinct clinical psychiatric entity. Since that time other observers[5-7] have augmented Kirby's contribution until today we recognize that marked agitation and depression, absurd delusional ideas, together with profound guilt-feelings constitute the psychotic menopausal (involutional) syndrome. In this illness, the menopausal or postclimacteric female is seen to be typically characterized as one who for years has been essentially selfish, narrowed in her interests, overreligious, frigid sexually or poorly adjusted to the sexual aspect of her marriage, narcissistic, and remarkably rigid in her social, moral, and ethical attitudes. Together, these attributes may be summated in the term "pre-psychotic personality." Such characteristics are not found so consistently or frequently among other women in the same physiologic era who develop a manic-depressive or a schizophrenic illness.

With the onset of a true involutional psychosis (melancholia), she becomes worried and depressed in spirits. She cannot sleep, is hypochondriacal, and preoccupied with somatic delusions. Finally she refuses to eat. When asked the reasons for her behavior and state of mind she offers bizarre absurdities that reveal her delusional and guilt-feelings.

It is largely this latter feature, the sense of guilt, real or delusional, over past minor and major infractions of her rigid code of behavior, and the agitation, which sets her apart from her depressed manic-depressive fellow-patient. Such autoflagellation of her emotional self-control results in an involved illness of many months' duration. When the delusional content is of a paranoid variety, the prognosis is less favorable.

A vast number of women go through the menopause with little or no subjective vasomotor complaints.[1] Of these, an overwhelming majority

whose personal attributes are suggestive of the pre-psychotic personality of an involutional melancholia patient do not become mentally ill. At least they do not enter mental hospitals. The known existence of ovarian insufficiency in all menopausal women makes it difficult to state that such deficiency is the *x* factor which determines whether or not a woman in her climacteric will become psychotic. However, this attitude is reflected in the writings of those[8, 9] who advocate substitution therapy for involutional psychoses as though it did not matter if vasomotor phenomena were present or not, and that the presence of labyrinthian psychic conflict is purely incidental.

Not infrequently a woman who has passed through her menopause without subjective distress will, five or ten years later, become psychotic. The history and features of her illness are such that a diagnosis of involutional melancholia is made. Papanicolaou and Shorr note that: "The menopausal type of (vaginal) smear is invariably present after the menopause, whether or not symptoms exist."[3] Regarding our patient above, the psychiatrist might paraphrase their statement: "The basic pre-psychotic personality exists before, during and after the menopause, whether or not a psychosis occurs." When the psychosis happens during the climacteric, the emotional trauma to that particular personality of the menopause experience itself, in a setting of heightened emotional response, may be the trigger mechanism for the psychosis. It follows, then, that the endocrine imbalance known to exist during physiologic gonadal involution may contribute to the emotional hypersensitiveness observed in the menopausal female. Substantiation of this is recognized when the diagnosis of involutional melancholia is made also in the psychotic male who is obviously in his involutional era. His pre-psychotic personality type characteristics are, broadly, the same as those of the female with the same psychosis.

In other words, to the menopausal female or the impotent male their physiologic involution assumes a symbolic significance. With emotional hypersensitiveness as a background, the stage is set, so to speak, so that emotional and personality factors are free to engage in a conflict marked by deep introspection, delusions, guilt-feelings, agitation, and depression.

It is common knowledge that such a woman is much more susceptible to minor insults to her pride or ego, and certainly she experiences more difficulty than ever before in coping with these, as well as with her major consciously recognized and/or long repressed emotional content of thought. Should the production of exaggerated affective responses be due to ovarian endocrine deficiency, as some workers believe,[8-10] it is a short step, according to such hypothesis, to indict the same mechanisms as the etiologic agent for the more profound gross mental aberrations we are discussing. Obviously, such emphasis entirely neglects the most cogent element in the psychotic pattern so produced: the basic pre-psychotic personality type, including early and later aspects. Brew and Davidoff have demonstrated that both the recent and remote personality features are etiologically important.

It is also true that the involutional era in a woman often marks the recurrence of one phase or the other of a manic-depressive illness . . .

possibly due to the same setting of emotional acuity which encourages the development of involutional melancholia. But, as has been shown, the prepsychotic type of the involutional melancholia patient is quite different from that of the woman who relapses into a manic-depressive illness. The previous attack of the manic-depressive patient has occurred, oftentimes, many years before the menopause. No ovarian insufficiency was operating then. Some other factor(s) precipitated the psychosis. And, it is so frequently seen in the reactivation of such an illness during or following actual menopause that emotional trauma has again precipitated the psychosis. To either type of potentially psychotic female such trauma may be the experience of the menopause itself . . . and all that it implies to the woman: loss of reproductive function, onset of middle age, etc. She may think of herself as a woman whose effective work in life has been completed and whose brightness in the family constellation is considerably dimmed.

It is generally recognized that involutional melancholia or involutional paranoia is preceded by a very long prodromal period, often of many years' duration.[6]

Again we emphasize that the minimization of hot flushes, chilly sensations and palpitations will cause the patient to be notably less disturbed *so far as she is disturbed over their presence*, and this improvement may aid her in taking a less distraught attitude toward her emotional conflicts. But this degree of improvement cannot be objectively regarded as setting the patient free from the shackles of her psychosis. Moreover, the occurrence of a menopausal psychosis (involutional melancholia) in a woman who does not complain of vasomotor nor sympathetic nervous system disturbances raises the question if the *x* factor, whatever it may be, is properly assigned solely to the field of endocrinology. Dynes[11] reports, significantly, the case of a woman whose vasomotor symptoms were relieved and her psychosis soon improved under endocrine therapy. She returned home; her hormone treatments were shortly discontinued and she soon suffered a recurrence of her hot flushes and other sensations. Likewise, she became considerably involved psychically. Upon returning to the hospital, she was given estrogen and her vasomotor symptoms disappeared, but her psychic aberrations continued more or less unabated.

Brew and Davidoff,[7] in an admirable discussion of the involutional psychoses mention that endocrine therapy cannot be expected to prevent or to cure a menopausal psychosis, because "where the individual's reaction to the menopause and its somatic influence is preponderantly affected, it allays only one factor in the total picture, not the superimposed one." They feel that the chief value of estrogens is seen in early *substitutive* therapy, in cases "where estrogenic or endocrine factors predominate in producing neurotic symptoms." Corroborating Shorr's comment previously mentioned, Brew and Davidoff point out that even among these cases, where the neurotic reaction pattern is influenced by the previous personality of the patient, little can be expected from substitutive hormonal therapy.

In addition to the substitutive aspect, estrogen preparations play a *stimulative* role when given, in adequate amounts, to the menopausal female. For this reason the physician should be exceedingly careful in his selection of patients for hormonal therapy. I agree with Brew and Davidoff in their belief that estrogens "may at times prove harmful if administered indiscriminately."

Our experience with psychotic menopausal and postclimacteric women at the New York Hospital, Westchester Division, White Plains, has led us to believe that a wrong and dangerous emphasis has been given to past and current conjectures of investigators regarding the value of ovarian hormonal therapy in the treatment of menopausal *mental* disorders. Repeatedly it has come to our attention that the unwitting physician in practice has attempted to treat his greatly upset neurotic menopausal or psychotic involutional patient with endocrine preparations when such patients have not been bothered by the usual neurocirculatory symptoms constituting the menopausal syndrome.

Under the circumstances just described, experience has demonstrated conclusively that among such severely neurotic, mildly or profoundly psychotic patients, hormonal therapy not only fails to help the patient but usually increases the emotional chaos the physician is trying to combat. This arises from the stimulation, by the estrogen, of ovarian and genital activity. These patients are, by virtue of their previous personality, in great conflict over their psychosexual desires and attitudes.

We recently had opportunity to check accurately this impression by experimental procedure in an effort to test the potency of a new synthetic ovarian follicular hormone* not yet available for general use. Twenty-six patients were selected for the study because their mental disorder had its incidence in the menopausal era, or subsequent to it, and was accompanied by many of the nervous symptoms outlined by Werner as being commonly associated with the menopausal syndrome; however, in contrast to similar studies made by other observers, it is of interest that none of them complained of the vasomotor phenomena of "hot flushes."

Of the 26 cases, 7 women had involutional melancholia, one had an involutional psychosis, paranoid type, while 15 were diagnosed as suffering from other psychoses. Two women had paranoid dementia precox (schizophrenia), while one was a Korsakoff's syndrome (alcoholic psychosis). The synthetic hormone's potency and general similarity to the natural estrogens was indicated by the production of "withdrawal bleeding" in 60 per cent of these patients with previous amenorrhea (one patient had not menstruated for twenty years), and by the alterations of the vaginal epithelium architecture as revealed by periodic vaginal smears. In six cases, or 23 per cent, certain so-called "toxic side-effects" were also noted: sensation of fullness in breasts, with enlargement, deeply-pigmented tender nipples and areolae, sensation of vulvar fullness, increased sexual desire, transient nausea, dysmenorrhea, persistent nausea, and diarrhea.

*4,4'—dihydroxy—α, β—diethyl stilbene (stilbestrol). Acknowledgment is made to E. R. Squibb & Sons for generous supplies of stilbestrol.

Bearing in mind the criticism by investigators who believe an involutional psychosis is due entirely to endocrine insufficiency, that poor therapeutic results with estrogen stems from inadequate dosage, the amounts of the synthetic hormone prescribed were considerably in excess of any as yet reported in the literature.

I recognize that many of the unfavorable toxic side-effects obtained with this particular preparation are not ordinarily perceived with the usual dosage of the natural hormone; however, it has been my experience that such effects as increased sexual desire and vague feelings of discomfort in the genital area are not uncommonly found with the moderate dosages of natural hormones now on the market.

Among the 12 patients (46 per cent) who showed no obvious awareness and/or offered comments attributable to the "withdrawal bleeding," such remarks were definitely of an unfavorable nature among 8 patients and conceivably favorable among 4.

The psychiatric clinical course during treatment revealed that 67 per cent remained unimproved and that 4 per cent became much worse.

A comparison of the patient's status before hormonal treatment began with the clinical picture following termination of treatment revealed that 43 per cent remained unchanged and that 38 per cent had become definitely worse. Of the 15 per cent that improved sufficiently to leave the hospital, it may be said that statistically the probability was in favor of ultimate recovery without any specific chemotherapy or endocrine administration.

CONCLUSIONS

The crux of the controversy hinges upon the question of whether the relief of the more aggravating vasomotor symptoms is justifiable at the expense of increasing or exaggerating certain other physiologic aspects which contribute to the psychosexual conflict that is partly responsible for the development of the psychosis or of the involved psychoneurotic burden.

It is our belief that it is not; and among such cases as are not characterized by distressing vasomotor phenomena, the employment of hormonal therapy solely to "cure" the mental aberrations of the involutional period appears entirely unjustifiable.

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ROENTGEN VISUALIZATION OF THE PLACENTA BY SOFT TISSUE TECHNIQUE

A Report of Two Years' Experience

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IN PREVIOUS articles,[1, 2] we have reviewed the literature dealing with localization of the placenta by various clinical and roentgen methods and have recorded our earlier experiences with direct visualization of the placenta by the use of the technique first described by Snow and Powell,[3] but used also for some years by Smith[4] who has as yet not published his results. After employing this method for a period of two years in 262 examinations, it seemed desirable for us to analyze our results statistically in an effort to determine the clinical value of this method.

It will be recalled that the method requires no preparation of the patient such as the injection of radio-opaque dyes into the urinary bladder or blood stream. It is entirely dependent upon actual visualization of the placenta on a lateral roentgenogram obtained with a technique that is not essentially different from conventional roentgenography. We have employed aerocystography in certain instances and occasionally confirmatory information has been obtained, but this report is based solely upon the primary method of actual visualization of the placenta. The location of the placenta can be easily determined in Fig. 1, since here the placenta is markedly calcified. We have not observed sufficient calcification actually to visualize the whole placenta in any of the other 261 examinations. However, in 6 there was slight (2) or moderate (4) calcification, but not sufficient to allow localization of the placenta on this basis alone. Therefore, calcification of the placenta is not an important factor in determining its location by this method. Usually the radiodensity of the placenta so closely approximates that of the uterine wall as to render differentiation of placental and uterine wall shadows impossible. But at the site of placental implantation, the uterine wall appears to be unusually thickened and this forms the basis of localization of the placenta by the soft tissue technique.

RESULTS

In 134 observations on 100 roentgenograms, we have found the average thickness of the uterine wall at the apex of the fundus and at its anterior and posterior walls during the last trimester to measure 1.24 cm. Snow and Powell[3] have shown that the combined placental and uterine wall shadow measures approximately 7.0 cm. at the point of greatest thickness and tapers off toward the periphery of the placenta. A typical example of this picture is shown in Fig. 2 where the placenta is clearly visualized on the posterior wall of the fundus. It is inconceivable that other soft tissue uterine or intrauterine shadows would be misleading or would introduce factors of doubt. It would be exceedingly rare, if possible, that an intramural or submucous

myoma could simulate the shape of the usually observed placental shadow. Retroplacental hemorrhage, as with premature separation of the normally implanted placenta, could not be differentiated from the normally attached placenta but might show increased thickness of the placental shadow. An accumulation of blood in

Fig. 1.—Lateral soft tissue roentgenogram of a primigravida obtained in the thirty-eighth week of gestation because of a clinical diagnosis of moderate hydramnios. This shows, instead, a large fetus presenting by the vertex, with its ventral surface facing the placenta, which is implanted over the whole of the anterior wall of the fundus uteri. The placenta can be clearly made out, since it is markedly calcified throughout. The uppermost arrows indicate the thickness of the posterior wall of the fundus; the upper pair of arrows on the anterior wall indicate the thickness of the placenta; the staggered arrows below these indicate in succession, the anterior wall of the fundus uteri, the rectus abdominis muscles, and the subcutaneous with the cutaneous tissues.

the uterine cavity between the chorion and uterine wall might conceivably increase the length of the placental shadow, but it would seem more likely that it would produce a second shadow as with a succenturiate placental lobe. We did not observe variations of this kind in the roentgenograms of the two cases in which a clinical diagnosis of premature separation of the normally implanted placenta was made.

Thus far, soft tissue lateral roentgenograms have been obtained on 259 patients; each of two patients were studied in a subsequent pregnancy, and a third patient was observed at two stages of a single pregnancy, making a total of 262 roentgen observations. These patients grouped according to race represent 149 colored, 87 white ward, and 23 private (white) patients. Eighty-seven examinations were upon primigravidas, 61 upon secundigravidas, and 114 upon patients of greater parity. The mean duration of pregnancy for the whole group at the time of x-ray study was 35.5 weeks with the range from 23.0 to 42.5 weeks. The figures for the group

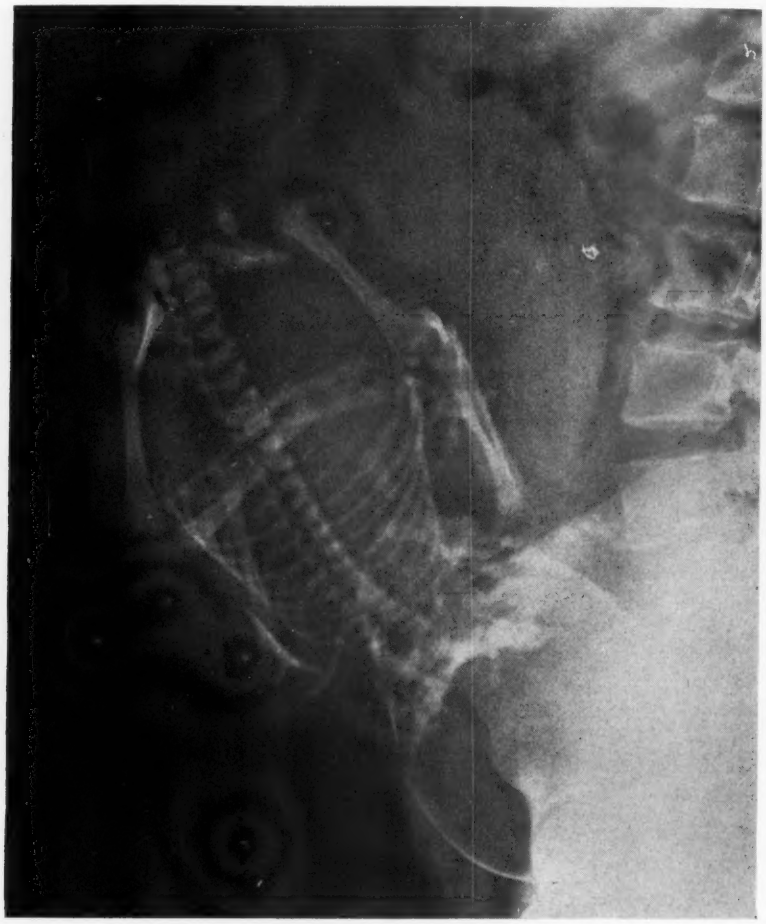

Fig. 2.—Soft tissue lateral roentgenogram of a young primigravida with a normal pregnancy, taken at term for experimental purposes, in order to develop the technique. The placenta is easily visualized on the posterior wall of the fundus. A lateral rather than the ventral surface of the fetus is directed toward the placenta. Osseous structures of mother and fetus are as clearly visualized as in conventional roentgenograms.

showing vaginal bleeding (92 cases) are somewhat less with a mean duration of 34.4 weeks and a range of 23.0 to 41.5 weeks. The eleven instances of actual placenta previa showed an even smaller average duration of pregnancy, 32.2 weeks with a range of 24 to 40 weeks. Contrary to what one might expect, the vaginal bleeding appeared earlier in pregnancy with the lesser degrees of placenta previa; i.e., at an average time of 34 weeks (30 to 40 weeks) in 5 cases of central previa, at 32 weeks (29 and 35 weeks) in 2 cases of the partial type, and at 30 weeks (24 to 35 weeks)

in 4 of the marginal variety. This point has not been previously touched upon, but our series is so small that the findings may well represent a sampling error.

The indications for roentgenography are listed in Table I. This shows that 92, or 35 per cent, of the examinations were made because of varying amounts of vaginal bleeding, i.e., because of clinical suspicion of placenta previa. The experimental roentgenograms, 47 or 18 per cent, were obtained in the earlier days of this study in order to develop the soft tissue technique. In the event a patient had been previously delivered by cesarean section, it was considered desirable to know whether the placenta in the subsequent pregnancy was implanted over the site of the previous uterine wound, since there is some reason to suspect[5] that if normal delivery is allowed in such instances, the incidence of rupture of the cesarean scar is higher than if the placenta is implanted elsewhere. In 17 patients in whom delivery by cesarean section was contemplated, the placenta was localized so that if anterior implantation was discovered, the operator might avoid, if he chose to do so, the site of implantation by selecting a low cervical or a classical incision, depending upon whether implantation was over the fundus or over the lower uterine segment. Moreover, he could be forewarned and could avail himself of additional precautionary measures in the way of transfusion. In the remaining 95 instances, 36.2 per cent, the roentgen examination was not requested primarily for localization of the placenta but rather, in most instances, because of suspected abnormality of the pregnancy. The soft tissue technique was nevertheless selected since the resultant roentgenograms furnish equally as good fetal bone detail as conventional roentgenograms and supply the additional information on placental location.

TABLE I. CLINICAL INDICATIONS FOR ROENTGENOGRAPHY

Vaginal bleeding	92
Probable multiple pregnancy	59
Experimental	47
Contemplated cesarean section	17
Previous cesarean section	11
Probable abnormal presentation	9
Probable fetal anomaly	6
Suspected death in utero	6
Hydramnios	4
Suspected postmaturity	4
Myomata uteri	3
Probable erythroblastosis fetalis	2
Unusual maternal obesity	1
Advanced extrauterine pregnancy	1
	262

Torpin,[6, 7] as well as many an older writer, has shown that the placenta is usually implanted over the relatively flat anterior or posterior uterine wall and that when it extends over the dividing line between anterior and posterior uterine walls, either laterally or across the apex of the fundus, it is likely to be one of a small group of abnormal placentas such as bipartita or spuria. Our relatively small group tends to confirm this impression, for we have never visualized the placenta on both anterior and posterior uterine walls and have never found it absent on both. Table II shows the location of the placenta with reference to segment and wall of the uterus at each examination. Implantation of the placenta on the lower segment was diagnosed whenever all or the major portion of the placenta was visualized in this region and when less than one-half appeared to be implanted above the level of the umbilicus. There were 26 such patients. All of these cases, it is important to note, do not represent clinical cases of placenta previa, nor were they all instances of vaginal bleeding. As a matter of fact, there were only 11 instances of clinical placenta previa in the group, while the remaining 15 were merely roentgenologic instances of low implantation of the placenta. There were only 2 cases

where clinical evidence of premature separation of the normally implanted placenta was present. Therefore, if cesarean section had been routinely performed on all cases of vaginal bleeding on the assumption that they had either placenta previa or premature separation of the placenta, that assumption would have been erroneous and cesarean section would have been unjustifiably performed in 85.87 per cent of the cases.

There is no significant difference in the incidence of implantation of the placenta over the anterior and posterior walls of the fundus, even in instances of vaginal bleeding, but the incidence of implantation over the anterior wall *of the lower uterine segment,* in our experience, is almost eight times as great as that over the posterior wall of the lower segment. This has been a repeated observation throughout this study, for in only 2 of the 11 cases of true placenta previa did implantation occur over the posterior wall of the lower uterine segment and internal cervical os. Beck and Light[8] and Jablonski and Meisels[9] have shown that implantation over the posterior part of the lower segment usually leads to an erroneous diagnosis of normal implantation when observed by indirect placentography. Since that method has a relatively high incidence of accuracy in the diagnosis of placenta previa (provided the pregnancy is advanced and the presentation vertex), we suspect that this indicates a low incidence of posterior wall placenta previa.

TABLE II. LOCATION OF THE PLACENTA AS DETERMINED FROM SOFT TISSUE LATERAL ROENTGENOGRAMS

SEGMENT AND WALL	BLEEDING CASES	NONBLEEDING CASES	TOTAL
Posterior fundus	33	70	103
Posterior lower segment	3	0	3
Anterior fundus	40	67	107
Anterior lower segment	12	11	23
Not visualized	4	22	26
Totals	92	170	262

The placenta was clearly visualized in 236 of the 262 observations, an incidence of 90 per cent. If the 8 examinations from which poor films resulted, had been repeated and granting that satisfactory roentgenograms would have resulted, the maximum visualization obtainable would have been 93 per cent. All causes of nonvisualization are listed in Table III, with the interfering factors. Hydramnios has proved to be the greatest interfering factor, but not an important one, since only one of these presented vaginal bleeding as a clinical finding, and placenta previa was not present in that case. Moreover, cases of acute hydramnios usually demand vaginal interference in the way of rupture of the membranes to relieve cardiac and respiratory distress, are frequently associated with fetal anomalies, and the avoidance of vaginal examination is not as urgent as in certain other conditions. Fur-

TABLE III. FACTORS WHICH DETER GOOD VISUALIZATION AND THE INSTANCES OF VISUALIZATION OF THE PLACENTA IN SPITE OF DETERRING FACTORS

DETERRING FACTORS	TOTAL NO.	NOT LOCATED NUMBER	LOCATED	
			NUMBER	INCIDENCE
Hydramnios	18	15	3	16.67%
Immaturity (less than 28 wk.)	13	2*	11	84.62%
Poor films	8	8	0	0.00%
Twin pregnancy	8	2	6	75.00%
Transverse presentation	6	1†	5	83.33%
Extrauterine pregnancy	1	1	0	0.00%
Totals	54	29‡	25	46.30%

*Nonvisualization attributed to (1) poor films and (2) twin pregnancy.
†Cause of nonvisualization included above under hydramnios.
‡Each of above three cases recorded twice.

thermore, the placenta was visualized in three instances in which hydramnios was diagnosed both clinically and roentgenographically. Immaturity is not such a hindering factor as we had previously suspected, for in 2 of 13 instances in which the pregnancy had advanced to only 23 to 27 weeks, nonvisualization in one instance was definitely due to poor roentgenograms and the other was attributed to the multiple pregnancy rather than to the early stage of pregnancy. Fetal position

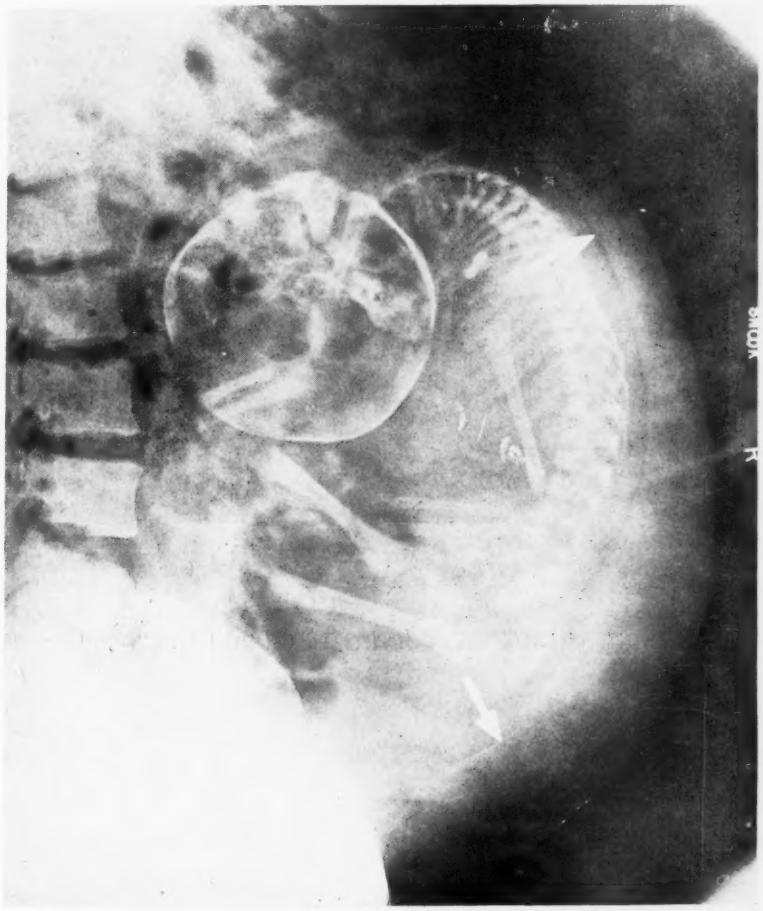

Fig. 3.—Roentgenogram of a multipara near term, who went into labor following premature spontaneous rupture of the membranes. Rectal examination upon admission to the delivery ward precipitated moderate vaginal bleeding. The placenta was visualized over the anterior wall of the lower uterine segment with its thickest region located by the lower arrow. The upper arrow is directed toward the anterior wall of the fundus, which is of normal thickness. The lumbar region of the fetal spine and the buttocks are flush against the placenta. This location of the placenta (placenta previa) was confirmed at the time of delivery by low cervical cesarean section.

does not in itself affect localization of the placenta by this method, for in only 1 of 6 cases of transverse presentation was the placenta not visualized and then because of hydramnios. Moreover, in each of 22 cases of breech position, the placenta was clearly visualized; the 5 instances of nonvisualization in association with breech positions were due to grossly poor films (3) and hydramnios (2). Except for the above recorded breeches and transverses, the extrauterine pregnancy which was diagnosed roentgenographically, and 2 cases of face presentation, all fetuses pre-

sented by the vertex. Clinical obesity of the mother is not listed as an interfering factor, because we failed to visualize the placenta in only one such instance and here hydramnios was associated.

In their original communication, Snow and Powell[3] contended that "in practically all cases, the ventral part of the fetus faces it (the placenta). In no instance was the fetal back flush up against it." We have not found this relationship to be a reliable criterion for location of the placenta. In fact, in at least 4 per cent of our series we would have made an erroneous diagnosis if we had relied upon the fetal position alone to furnish the information on placental location, for in 7 instances in which the fetus presented by the vertex and in 4 in which it presented by the breech, some part of the back of the fetus was directed toward the placenta. Fig. 3 is a typical example of the dorsal surface of the fetus being directed toward the placenta. While it is true that the ventral surface of the fetus frequently faces the placenta, it is not uncommon to see the lateral fetal surface directed toward the placenta.

An attempt to check clinically the location of the placenta, as originally diagnosed by x-ray, was made in 53 (20.4 per cent) of the 261 pregnancies and no roentgen errors were detected. Moreover, in the cases not checked clinically, the subsequent course of the pregnancy and labor was in strict conformity with the roentgenologic diagnosis. The results of the clinical checks are recorded in Table IV. It was considered that placenta previa was present if, on vaginal examination, the lowermost margin of the placenta could be palpated within 5 to 6 cm. of the closed internal cervical os, whereas failure to reach the placental margin at this level was regarded as confirming the roentgenologic diagnosis of "no placenta previa."

TABLE IV. CLINICAL MEANS OF CHECKING THE ROENTGENOLOGIC LOCATION OF THE PLACENTA WITH RESULTS CONFIRMING THE LATTER

CLINICAL METHOD CONFIRMING	NONBLEEDING CASES	BLEEDING CASES	TOTAL
Cesarean section	13	7	20
Vaginal examination	0	31	31
Vaginal examination and cesarean section	0	2	2
Totals	13	40	53

In our hands, the greatest usefulness of the soft tissue technique has been in cases of vaginal bleeding, more particularly in those in which placenta previa could be ruled out, the whole of the placenta being visualized above the level of the iliac crests. There were 81 such patients, making up 88.0 per cent of the cases presenting a history of vaginal bleeding; by means of the method it was possible to spare these women the hazards of an intrauterine digital examination to rule out placenta previa. Of course, vaginal examination may be necessary to determine such causes of vaginal bleeding as cervical, decidual, and placental polyps, erosions of the cervix, vaginal varices, deciduomas, and cervical malignancies, but this can be done by speculum examination and without interfering with the integrity of the cervical canal.

We believe that the method might find some usefulness in determining the relative soundness of the uterine wall in the region of a previous longitudinal cesarean wound, and attempted to visualize anterior wall thickness in 10 patients previously delivered by classical or longitudinal low cervical cesarean section. One of the two in which definite thinning of the anterior uterine wall was found is shown in Fig. 4. In the other instance, the patient was allowed vaginal delivery, and intrauterine examination thereafter revealed a deep furrow in the anterior wall, at the site of the previous classical cesarean section. Only positive findings of this kind will be of value in cases previously delivered by cesarean section, while negative observations will not preclude the absence of a weak cesarean scar. If it were possible to ascertain the site of the previous cesarean incision, and then in the subsequent pregnancy to determine dextro- or levorotation of the uterus, the opportunity to

visualize the site of the previous incision would be greatly increased by positioning the patient in the true lateral, or in an oblique position, in order to bring this site into the plane parallel to the film.

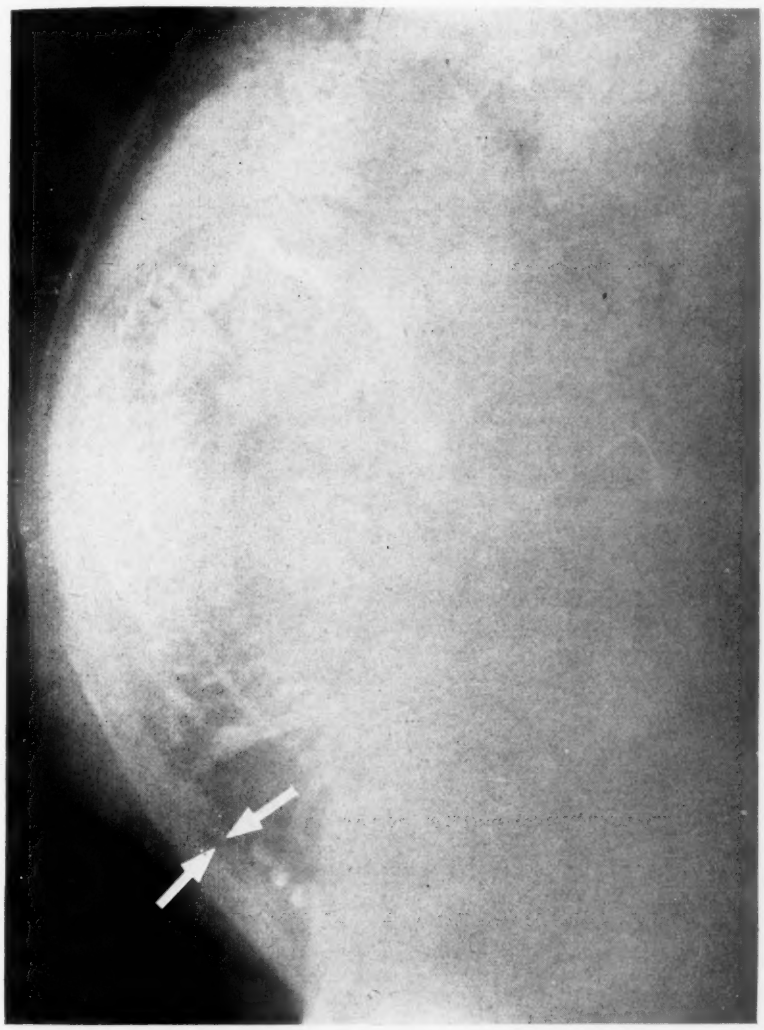

Fig. 4.—Roentgenogram of a secundipara, whose first delivery was effected by classical cesarean section, on account of fulminating pre-eclampsia. The post-operative course was moderately febrile, but thought to have been due to acute bronchitis. The roentgenogram shows irregular thinning of the anterior uterine wall. The area located by the arrows was found at operation to measure less than 3.0 mm. in thickness. The placenta is located on the posterior wall of the fundus.

CONCLUSIONS

1. The placenta was clearly visualized by soft tissue roentgenography in 236, or 90 per cent, of 262 observations on 259 patients, in 261 pregnancies.

2. The greatest factor interfering with visualization was found to be hydramnios, and accounted for nonvisualization in 5.73 per cent of

the roentgenograms. Unsatisfactory x-ray films were obtained in 3.05 per cent of the cases, and it was impossible to visualize the placenta in 2 of 8 cases of twin pregnancy. Immaturity, provided the pregnancy has advanced beyond the midpoint, and abnormal presentations and positions are not hindering factors in visualization.

3. Calcification of the placenta is rarely extensive enough to aid in localization of the placental site. No other adjuncts to actual visualization were found. Fetal position is not a reliable criterion of the location of the placenta.

4. No errors in roentgenologic localization of the placenta were found in the 53 instances which were checked by reliable clinical methods.

5. The placental implantations were almost equally divided between anterior and posterior walls of the fundus. However, with low implantation, essentially eight times as many placentas were found implanted on the anterior as on the posterior wall of the lower uterine segment.

6. The average thickness of the walls of the fundus uteri near term measured 1.24 cm. on the roentgenograms which were made at a distance of 42 inches.

7. Only 11 (12 per cent) of 92 cases of vaginal bleeding were found roentgenographically and clinically to have true placenta previa; 15 other cases presented merely x-ray evidence of low implantation of the placenta, without the usual clinical signs.

8. Soft tissue roentgenography in obstetrics finds its greatest usefulness in those cases of vaginal bleeding where the whole of the placenta can be visualized above the level of the iliac crests and these constitute the great majority, 88 per cent, of the instances of vaginal bleeding in the latter months of pregnancy.

We are deeply indebted to Mr. J. C. Fletcher, Chief Technician of the Department of Roentgenology, for his untiring efforts in developing the soft tissue technique in our x-ray laboratory, and for his valuable aid in obtaining photographic reproductions of the roentgenograms; also to Mr. Arthur W. Fuchs of the Medical Division of the Eastman Kodak Company, for expert aid with the photographic reproductions.

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CHRONIC NEPHRITIS AND PREGNANCY FATALITIES IN PHILADELPHIA*

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THIS study represents part of the work of the Philadelphia Maternal Mortality Committee, under the Chairmanship of Dr. Phillip F. Williams. It consists of an analysis of the fatal cases of chronic nephritis complicated by pregnancy occurring in Philadelphia from Jan. 1, 1931, to Dec. 31, 1938, an eight-year study.

The statistics were analyzed for answers to the following questions:

1. What is the incidence of chronic nephritis in relation to other causes of obstetric death?
2. What are the biologic characteristics of this disease in its fatal form?
3. Were these deaths all unavoidable and, if not
4. What avoidable factors can be controlled by the medical profession?
5. What is the ideal management of a case of chronic nephritis complicated by pregnancy, in the light of our present-day knowledge?

The term chronic nephritis is vague and includes three forms:

1. Chronic glomerulonephritis.
2. Nephrosclerosis.
3. Nephrosis.

There has been no attempt to differentiate these forms. To do so would be impossible from the data available in the hospital and mortality committee records. As will be seen from the detailed analysis, the majority, if not all, were nephrosclerotics; at least, hypertension and vasospasm were present in every case.

The conclusions of the committee were followed in every case even when I disagreed with the assignment of responsibility or diagnosis. Although a group of human beings may occasionally err, in the long run the findings of the Committee will be found accurate.

INCIDENCE

The series is composed of 44 cases. Forty died in hospitals, of which two died while being transported to the hospital (one from New Jersey) and were pronounced dead on arrival. These deaths occurred in 20 of the 26 hospitals in Philadelphia, including all the medical college hospitals. Four died at home.

During the eight-year period, there were 1,349 puerperal deaths, so that the incidence of fatal nephritis is about 3.25 per cent of all deaths.

Table I also shows the decreasing maternal death rate. Chronic nephritis causes only about 3 per cent of all deaths.

It must be remembered that only primary mortality is considered in this paper. Stander has shown that about 40 per cent of nephritics that recover die within the ten-year period following delivery. Thus the problem is greater than the primary death rate would indicate.

*Read at a meeting of the Obstetrical Society of Philadelphia, March 7, 1940.

Age is an important factor. The proportion of chronic nephritis increases rapidly after thirty-five years. Until then the incidence of the disease is about stationary, regardless of age.

In this series multiparity does not seem to increase the incidence as much as commonly thought. From the fifth pregnancy on, the rate about doubles, but beyond this increasing parity does not cause an increasing incidence.

TABLE I. RATIO OF CHRONIC NEPHRITIS TO OTHER DEATHS

YEAR	TOTAL BIRTHS	TOTAL PUERPERAL DEATHS	NO. OF CHRONIC NEPHRITIS	% OF CHRONIC NEPHRITIS
1931	33,773	248	10	4.0
1932	31,766	239	7	2.9
1933	29,241	152	10	6.5
1934	29,485	164	7	4.2
1935	29,723	156	2	1.2
1936	29,396	174	3	1.7
1937	29,771	117	1	0.8
1938	30,447	99	4	4.0

TABLE II. RATIO OF CHRONIC NEPHRITIS TO OTHER DEATHS BY AGE GROUPS

AGE	15-19	20-24	25-29	30-34	35-39	40-44	NO RECORD
All deaths	52	376	335	281	226	77	2
Chronic nephritis	2	2	10	8	13	8	1
Per cent	3.9	0.5	2.9	2.8	5.7	10.4	

Incidence increases after 35 years.

TABLE III. RATIO OF PARITY TO CHRONIC NEPHRITIS

PARA	CHRONIC NEPHRITIS	PER CENT	ALL DEATHS
1	9	1.9	474
2	8	4.0	198
3	4	2.8	141
4	1	0.9	106
5	6	7.1	84
6	3	8.5	35
7	2	5.5	36
8	2	4.1	48
9	1	4.1	24
10	3	9.6	31
11	3	21.4	14
12	1	7.7	13
No record	1		145
Totals	44		1,349

Incidence increased from para v upward.

CLINICAL CHARACTERISTICS

Twenty-five of these patients had a history suggestive of previous toxemia. The most extreme example is that of an 18-year-old para ii who was permanently blinded by toxemia at the birth of her first baby, one and a half years earlier. When she became pregnant again she reported to the prenatal clinic at twenty-six weeks with a blood pressure of 210/140. Unfortunately, the seriousness of the situation was not recognized by the physician on the first visit, and she was admitted to the hospital two weeks later in fatal coma and convulsions.

A less dramatic, but just as significant, history was that of a 43-year-old para viii who gave a history of six or seven miscarriages, refused to consult a physician until she was brought into the hospital, twenty-four weeks pregnant, in convulsions and died six and one-half hours later.

Hypertension was the one symptom common to all and is rightly accepted as the chief and earliest symptom. The majority (32 cases) had a systolic pressure between 140 and 200. Two had pressures as high as 300 and over and only two had a pressure between 130 and 140 when first observed. One of these died of adherent placenta, post-partum hemorrhage, and shock. The other showed a rising pressure which reached 204 at delivery when she developed eclampsia, coma, uremia, and died ten days post partum.

TABLE IV. FREQUENCY OF SYMPTOMS

Hypertension		44
Edema		36
Ascites and hydrothorax	1	
Pulmonary	1	
Cerebral	1	
Coma		34
Convulsions	22	
Albuminuria		33
Headache		28
Nitrogen retention		23
Nausea and vomiting		21
Obesity		20
Amaurosis		20
(Eye grounds examined in 8)		
Hemorrhage		13

All but five showed convulsions and coma

Edema was the next most common symptom and usually generalized over the body. Pulmonary and cerebral forms were probably more common than actually noted, but hydrothorax and ascites were unique.

Coma and convulsions were almost as common as hypertension; in fact, there were only 5 deaths in which neither convulsions nor coma occurred. These exceptions were due to:

1. Post-partum hemorrhage and shock following cesarean section.
2. Cesarean section followed by anuria and fever.
3. Retained placenta with death under anesthesia.
4. Cerebral hemorrhage, post partum, in a mild nephritic with a blood pressure of 150/100.
5. Acute cardiac dilatation five days post partum.

Albuminuria, although not common to all, was one of the most significant signs. It developed early, even before hypertension in three cases, and was a persistent danger sign.

Headache, gastric symptoms, and nitrogen retention were all observed as late symptoms and need no comment.

Obesity was present to a remarkable degree and far out of proportion to the usual occurrence. Four patients weighed more than 200 pounds. Twenty were noted as obese, 7 as average, 4 as thin. In 13 there was no record of weight or comment as to size. This high incidence of obesity would suggest a serious disturbance of metabolism and the endocrine system as an underlying cause of chronic vascular and kidney disease.

Eye grounds were rarely studied; the ophthalmoscope was used only eight times although amaurosis was recorded in 20 cases. This is an error on the part of the attending physician. The presence of retinitis or hemorrhage will show at once the seriousness of the case.

Uremia was the cause of death in the great majority, but hemorrhage was a common complication (13 cases). This is primarily due to the effect of nephritis on the placenta causing abortion (3 cases), miscarriage (1 case), premature placental separation (3 cases), and placenta previa (1 case, probably frank bleeding of premature separation).

TABLE V. CAUSES OF DEATH

Uremia		30
Hemorrhage		13
Ante partum	5	
Post partum	5	
Cerebral	1	
Liver	1	
Skin (purpuric)	1	
Acute heart failure		3
Acute yellow atrophy		2
Single cause		40 cases
Combined causes		4 cases

There were also 4 cases of post-partum hemorrhage and 3 of the patients showed hemorrhage in unusual situations, including the brain, liver, and the skin in the form of purpura.

More emphasis should be placed on hemorrhage and shock when considering chronic nephritis.

The liver and heart are also damaged in this disease as shown by 2 cases of acute yellow atrophy, 1 of massive hemorrhage of the liver, and 3 cases of acute cardiac dilatation.

METHOD OF DELIVERY

In severe chronic nephritis termination of the pregnancy is the indicated treatment. In this series termination was advised twenty-seven times; in 5 cases the advice was refused and in one case spontaneous delivery occurred before induction could be started.

Eight patients were delivered by cesarean section (7 abdominal and 1 vaginal). Thirteen had induction of labor, of which 7 delivered spontaneously, 3 by version, 2 by forceps, and 1 by therapeutic abortion.

The need of relief in these recognized desperate cases accounts for the high incidence of cesarean section. Three cesarean sections were performed after conservative treatment failed; 1 was for premature separation of the placenta and 4 because of the severe toxemia which required prompt termination of the pregnancy.

TABLE VI. METHOD OF DELIVERY

Abortion		3
Normal		17
Version		3
Forceps		2
Cesarean section		7
Vaginal cesarean section		1
Undelivered		10
Induction		13
Puncture membranes	6	
Medical	3	
Pack	1	
Bag and pack	1	
Puncture and bougie	1	
Dilatation and evacuation	1	

Including cesarean section total number of pregnancies terminated is 21.

TABLE VII. BABIES

BORN ALIVE	STILLBORN	DIED	UNDELIVERED	UNKNOWN
14	11	5	10	4

Infant mortality rate 68 per cent.

AVOIDABLE FACTORS

Fifteen of the cases were considered nonpreventable tragedies by the committee because the disease was too far advanced to save the patient.

Twenty-nine, or 66 per cent, were thought to be avoidable. Nineteen (43 per cent) were due to the ignorance or indifference of the patient, usually because she did not report for prenatal care or did not follow her medical advice as to proper bed rest, hospitalization, etc.

TABLE VIII. PREVENTABILITY

Unavoidable			15
Preventable			29
Patient		19	
Lack of prenatal care and ignorance	14		
Refusal to follow advice	5		
Physicians' errors		10	
Delay in proper treatment	7		
Inadequate prenatal care	1		
Neglect of a home case	1		
Error in surgical judgment	1		

66 per cent avoidable, 43 per cent due to patient, 23 per cent due to physician.

Ten deaths (23 per cent) were considered due to an error of judgment on the part of the physician, chiefly because he refused to recognize the seriousness of the case. An example of this was the case of a para i whose condition was recognized at the thirtieth week of pregnancy, and she was hospitalized for three periods of nineteen, eleven, and eleven days, at the end of which time labor was induced. It was too late; she died of uremia eight days after the birth of the stillborn child. Two deaths were due to medical neglect and one to an error of surgical judgment in a case of premature separation of the placenta with hemorrhage.

COMMENT

These facts show the necessity for review of the obstetric care offered our patients. Even in a serious disease like chronic nephritis most of the deaths are unnecessary and about one-fourth are due to errors of the attending physician. Therefore, the following schedule of study and treatment is offered as a minimum standard that will provide thoroughly adequate care. The object is to make it so practical that it can be used in a small hospital with minimum laboratory facilities as successfully as in a large institution with every resource. All but one of the studies can be done by a capable physician in the patient's home.

When the patient first reports for obstetric care, the history should elicit evidence of previous kidney or arterial disease, including repeated abortions. Usually the patient will volunteer the information before she is asked. She should also be observed for obesity; and if it is present to any great degree, she should be classed as a potential nephritic.

Once the diagnosis of chronic nephritis is made it should be remembered that the essential pathologic lesions are vasospasm of the arteries and progressive kidney damage with secondary effects on the other organs as the liver, heart, and brain.

There are only two methods available in the management of this disease:

1. Rest, salt-poor and low-protein diet, and maintenance of fluid balance prevent edema and carry the pregnancy as far along as possible to obtain a viable child.

2. If this fails or the case is severe the pregnancy should be terminated to save the mother's life.

In order to evaluate the severity of the disease, the following studies should be made: (1) Blood pressure; (2) weight; (3) physical examination for edema and cardiac damage; (4) fluid intake and output; (5) urinalysis; (6) renal function tests: (a) Fishberg concentration and (b) fractional phenolsulphonephthalein test as described by Stander; (7) eye ground examination; and (8) blood total nonprotein nitrogen for nitrogen retention.

These are simple standard examinations that can be done by any physician, with the exception of the single blood chemistry estimate, and will give information of ample degree of accuracy to indicate termination of pregnancy. They should be repeated as often as necessary to reach accurate conclusions.

The following may be listed as serious danger signs and positive indications for immediate interruption:

1. Rapidly rising blood pressure or a systolic pressure of 180 or above.
2. Amaurosis with retinitis or retinal hemorrhage.
3. Persistent albuminuria, increasing in quantity.
4. Nitrogen retention, nonprotein nitrogen above 45 mg. per 100 c.c.
5. Increasing edema or marked edema that does not respond to treatment.
6. Signs of cerebral irritation as persistent headache, gastric symptoms, epigastric pain.

If coma and convulsions develop, then delay has been too long and the patient should be treated as an eclamptic. Careful study will bring about an early recognition of the serious sign before the disease reaches a desperate condition.

In selecting the method for interrupting the pregnancy, two facts should be kept in mind: (1) the danger of hemorrhage, and (2) nephritics are more likely to develop shock than ordinary normal pregnant women.

The following methods are suggested:

First Trimester.—Abdominal hysterectomy where patient's condition warrants the risk, otherwise therapeutic abortion with later sterilization.

Second Trimester.—Puncture of membranes and bougie with later sterilization or abdominal hysterectomy if physical condition warrants the risk; although the bougie has a greater risk of infection, it is a surer method of induction.

Third Trimester.—Puncture of membranes and medical induction using not more than 20 gr. (1.3 Gm.) of quinine or pitocin in only 0.1 c.c. doses.

If rapid evacuation is imperative, classic cesarean section.

After coma and convulsions develop, the patient should be treated as an eclamptic. Conservative measures should be used, no surgery attempted, until she is out of her convulsive state, then the pregnancy terminated.

SUMMARY

The analysis of 44 fatal cases of chronic nephritis complicated by pregnancy shows that two-thirds of the primary mortality is preventable, of which two-thirds are due to lack of prenatal care and ignorance of the patient and one-third due to errors of judgment on the part of

the physicians. The chief error in medical care was failure to recognize the seriousness of the situation and failure to terminate pregnancy promptly.

In addition to the usual symptoms of the disease, the frequency of obesity and hemorrhage is demonstrated as serious complicating factors. The failure to study eye grounds is noted with the recommendation that an ophthalmoscope should be part of the standard equipment of a maternity and that the eye grounds should be studied by the obstetricians.

A minimum standard is offered for the diagnostic study and evaluation of the disease with definite indications for termination of pregnancy.

I wish to express my thanks to Dr. Williams for assistance and guidance and to Mrs. William Reishtein and Miss Malkiel whose help in obtaining data and preparing statistics was invaluable.

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DISCUSSION

DR. PHILIP F. WILLIAMS.—The diagnosis of nephritis in pregnancy is a difficult one, so that it is possible that some of the cases that Dr. Paxson reported may not have been this disease. Likewise, I would not be surprised if some cases of chronic nephritis which came before the Committee have been missed for several reasons. In the first place some toxemias simulate an acute toxemia overlying a chronic nephritis. In the second place due to the lack of the history and other findings just referred to, patients with chronic nephritis have probably been put down as true toxemia without knowledge of the previous renal lesions. It is difficult to establish the diagnosis of chronic nephritis in the toxemic woman who first is seen after six and one-half months.

There is a far broader implication in this paper, however, namely, the prevention of pregnancy in women with a constitutional impairment of this type. With further education of the public regarding periodic health examinations more and more women will seek premarital and preconceptional examinations. When this happy day arrives, we may be able to determine certain cases in which the occurrence of pregnancy would be detrimental, and to these could be suggested the use of contraceptive measures. Not all patients with chronic nephritis will need to have pregnancy prevented but the knowledge of its pre-existence when pregnancy supervenes will enable us to supervise a pregnancy to a far better degree.

DR. EDWARD WEISS.—The subject of kidney disease and pregnancy has been a confused one for several reasons: first, because of the old belief that the toxemia of pregnancy was of "nephritic" origin and that the convulsive seizures were "uremic"; second, because of the failure to differentiate glomerulonephritis, pyelonephritis, and essential hypertension complicated by pregnancy; third, because of the attempt to remedy this situation by the invention of such terms as substandard or low reserve kidney; fourth, because of the lack of accurate knowledge as to the remote effects of the toxemia of pregnancy on the cardiovascular-renal system of the mother.

When we first became aware of the importance of high blood pressure from a clinical standpoint, it was thought that arteriosclerosis was responsible and that the patient was doomed to die of kidney disease. About the turn of the present century, largely due to the efforts of Allbutt in England, Huchard in France and Janeway in America, we learned that most hypertension was of nonrenal origin, that is, it was of the so-called "essential" variety. Instead of being caused by

arteriosclerosis, the relationship was just the reverse, for it was a vasospastic disorder which caused thickening and stiffening of the blood vessels, and hence, was responsible for the arteriosclerosis. Just when we felt that we had emancipated ourselves from the idea that the kidney was responsible for hypertension, however, Goldblatt, by his very ingenious experiments on dogs, led us right back to the renal origin of hypertension.

Views on the nature of kidney disease and the toxemia of pregnancy have run a similar circular course. Originally, it was held that toxemia was nephritic in origin and then gradually we came to the opposite conclusion, that the toxemia of pregnancy was not of renal origin but instead that it arose from some unknown toxic source and resulted in damage to the kidneys. Largely through the efforts of Herrick and Tillman we learned that not only did the toxemia of pregnancy injure the kidneys but that more often it resulted in irreparable damage to the vascular system so that perhaps in one-half of all cases of toxemia of pregnancy, hypertensive-vascular disease would certainly follow within a period of a few years. Yet now Peters of Yale is once more insisting upon the importance of a renal lesion in the background of toxemia of pregnancy. He is particularly concerned with pyelitis and pyelonephritis as predisposing factors, but there is as yet no widespread clinical confirmation of his views.

In regard to Dr. Paxson's suggestions about treatment I would raise one question in regard to limitation of protein. The restriction of proteins in patients with all forms of kidney disease is a hang-over from the days when we thought that protein was injurious to the kidneys. We have changed our ideas considerably in this regard and Strauss has even suggested in his recent study that instead of withholding protein from the patient who shows evidences of toxemia, proteins are necessary in large amounts. The same thing is true in kidney disease with a loss of a large amount of protein in the urine and a consequent depletion of the blood protein. Here proteins must be given in larger instead of smaller quantities than normal.

DR. OWEN J. TOLAND.—The third table showed that 40 women died of chronic nephritis but only 9 were primiparas. The presumption might be that in their previous pregnancies, most of the 29 multiparous patients showed some evidence of hypertensive disease. The easier place to have handled this problem would have been at the end of such previous pregnancies. I think it is merely a question of a few more years until abdominal sterilization will be offered routinely for such patients.

DR. JAMES LEWIS.—I would like to ask what constitutes an unavoidable case. If the patient had adequate prenatal care and there was no delay in instituting treatment, where was the unavoidable factor?

DR. PAXSON (closing).—First, what is the unavoidable case? A woman with a systolic blood pressure of 150 delivered spontaneously and eight days later dies of cerebral hemorrhage, ought to be considered unavoidable. Unless you terminate all pregnancies with a blood pressure over 130, I think you must consider that case as unavoidable. Then you will always have that group of women who prefer to stick by their religious convictions. We class that as unavoidable, believing that a human being has the right to follow her religious belief on the subject. A case of premature separation of the placenta is another example; a woman with a moderately elevated blood pressure and slight evidence of chronic nephritis develops placental abruptio, is rushed to the hospital, and section is done, but she dies. I think that is unavoidable.

I agree with Dr. Toland. Twenty-five of these women gave histories of one type or another suggestive of kidney and arterial damage. On the other hand, the others did not, and possibly a history of previous kidney damage would have been obtained could we have interviewed the patients before they died, but we only had hospital data to go by, and some of the records were not as complete as they might have been.

THE EFFECT OF ESTROGENS ON TRUE PRE-ECLAMPSIA AND ECLAMPSIA

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INCLUDING A BRIEF NOTE BY M. M. O. BARRIE, B.Sc., LONDON, ENGLAND

IT IS generally recognized that physiologic pregnancy is largely under hormonal control. It should not be surprising, therefore, if many of the features of pathologic pregnancy are evidences of hormonal dysfunction or uncontrol. For example, in 1935 the Smiths[1] reported that the blood of eclamptic patients revealed low values for estrin. My studies supported this conclusion and I began to treat eclampsia with this in mind. As improvement appeared to follow such therapy,[2] I have continued it and present several protocols here in the effort to stimulate further interest in the method. It should be noted that the original finding of the Smiths has since been confirmed by Muhlbock[3] and that Siegler[4] also has reported a good result after the use of estrogens in pre-eclampsia.

In my first paper on this therapeutic method, I gave the protocols of one pre-eclamptic and 2 eclamptic women treated with estrogens. Herewith are the records of 7 more pre-eclampties and of 2 convulsive eclamptic patients. All other true pre-eclamptic patients have reacted well to this treatment, but the cases presented are illustrative of what may be expected.

CASE 1.—Mrs. F., aged 27 years, had had a normal pregnancy three years before, followed by phlebitis. She was first seen Jan. 21, 1937 with a recurrent phlebitis in one leg, the first suggestion of another pregnancy. Her last period had begun on Dec. 25, 1936. There was vaginal bleeding on January 23, with pelvic pain and severe sacral backache. This was promptly controlled with wheat germ oil. The phlebitis soon subsided. Her weight at that time was 117 and her blood pressure 114/66. Her urine was clear. She stopped taking the wheat germ oil soon after her first threated abortion, but was forced to return to it temporarily on May 21, as uterine tenderness had returned. On July 16 her weight was 136 and blood pressure 108/68. She had had no wheat germ oil since the end of May. On August 3 her weight was 146, her pressure 132/76, and there was considerable edema of the face, fingers, and left leg, as well as much visual disturbance. She was promptly taken off salt and milk. By the seventh her weight had fallen one pound, her pressure was 118/80, the edema had decreased, but a few uterine cramps had appeared. She felt well until September 11, when her weight had increased to 153, her pressure was 126/86, there was less edema, but the urine showed a 2-plus albumin in a two-basin sample. On the twelfth she developed a persistent parietal headache which lasted for three days, her pressure soon rose to 162/100, and she had epigastric distress, blurred vision, and backache, but no uterine contractions and no edema. She was given ¼ gr. of morphia and 10,000 I.U. of progynon B at 8:00 A.M. on the sixteenth of September. By the next day her headache had disappeared but she was somewhat dizzy. Her eyesight improved rapidly. She passed a mere 3 ounces of urine during the night before 7:00 A.M., but passed as much more in the next two hours. Her blood pressure at 8:00 A.M. was still 152/98 and her urine showed a 3-plus albumin. The progynon B was repeated in the same dosage and medical induction was begun, with artificial rupture of the membranes at 9:00 A.M. on the

eighteenth. By 11:00 A.M., the pressure was unchanged, but there was some blurring of vision again and photophobia. She had passed 20 ounces of urine since 9:00 A.M., having a 3-plus albumin and a specific gravity of 1.011. At 2:30 P.M. her blood pressure was 138/88 and uterine contractions began. By 6:00 P.M. her pressure had climbed to 170/116, she had passed but two ounces of urine in the last three hours and there was a 2-plus albumin in this. She was slightly drowsy henceforth, and in hard labor. At 8:30 P.M. she was delivered of a 4-pound 11½ ounce healthy male child. Just prior to delivery her pressure had reached 170/112. Ten minutes after the birth it was 124/76, but there was no evidence of shock. The placenta was small and showed 10 large round white infarcts penetrating its whole thickness. The progynon B was repeated and ⅙ gr. of morphia was given. She had an easy night. Next day she voided freely, had a slight edema of the fingers and toes, no complaints of any kind, and was bright and cheery. Her pressure hovered about 120/80 on several readings. A catheter urine showed 3-plus albumin still. The edema had increased by nightfall; accordingly 10,000 I.U. progynon B were given. The edema had disappeared by morning. She had an uneventful recovery and is still perfectly well with a blood pressure of 126/70.

CASE 2.—(Courtesy of Dr. J. F. Simpson.) In her first pregnancy Mrs. P., aged 30 years, had had blindness in one eye for two weeks following delivery. In the ensuing seven years she had five spontaneous abortions and miscarriages at one to six months of gestation. In 1937 a pregnancy characterized by severe "preeclampsia" occurred. An induction was done and a living child was secured. Pulmonary embolism followed, associated with phlebitis of the left leg.

Her last menstrual period began on June 2, 1938. The pregnancy proceeded uneventfully in the early months. However, she complained of dizziness and visual specks on Sept. 23, 1938, when she had a blood pressure of 140/80, but no albuminuria. Her physician gave her epsom salts every second day as well as a salt-free diet, and she carried on normally until a transient left-sided hemiparesis developed on Jan. 2, 1939, associated with a clear urine and a blood pressure of 120/70. On January 25 the pressure was 140/90. On February 8 the pressure had climbed to 160/98, the edema was considerable, and there was a 2-plus albumin in the urine for the first time. On February 17 her pressure was 180/105, her urine showed 4-plus albumin, there was much edema and visual disturbances were marked. Next day her blood estrin was negative and she was put to bed and given 10,000 I.U. of progynon B intramuscularly. Her pressure was 185/105. On February 19 the progynon B was repeated at the same dosage, a good diuresis occurred in the night, and her pressure fell to 175/100. Her visual symptoms promptly cleared. On February 20 another 10,000 I.U. of progynon B were given and the pressure soon fell to 175/94. On February 21 she went into labor spontaneously and in five hours delivered a 5-pound baby boy. On March 3 her pressure was 134/70. After her uneventful recovery an x-ray sterilization was done. On March 17, 1939, her blood pressure was 142/82, and the mother and child have been well since.

CASE 3.—In her first pregnancy, Mrs. B., aged 33 years, had had toxemia with repeated hemorrhages. Her last period began July 25, 1939. She was first seen Feb. 28, 1939, when seven months pregnant. She had put on 47 pounds of weight in this pregnancy up to that time, attaining a weight of 193, had a blood pressure of 118/70, and had edema of the legs extending nearly to the hip. She was taken off of salt and milk. Her blood estrin was negative. By March 7 she had developed frequent occipital headaches, had gained to 195 pounds, had a pressure of 130/76, and had a 2-plus albumin in the urine. She was then given 50,000 I.U. of progynon B and three tablets per day of progynon-DH. On March 11 there was only a trace of albumin in the urine, much less leg edema; her weight was 194 and her pressure 138/76. The headaches were unchanged. The dose of 50,000 I.U. of progynon B was repeated. On the sixteenth she received 20,000 I.U. of progynon B. On the twenty-first her weight was 197, her pressure 122/74, urine clear, the headaches had gone, and she volunteered she felt "marvelous." On the twenty-eighth there was enormous edema of both legs and one of them was "numb to the hip." Her weight was only 196, however, and her pressure 128/80. There was

a smaller urine output and a 2-plus albumin. She was given 50,000 I.U. of progynon B. On April 1 her weight was 200, her pressure 130/74, both legs had improved, but the headache had returned. Her measured urinary output for the preceding four days had been about 1,000 c.c. per day. She had passed only 400 c.c. in the twelve hours prior to her visit to the office, although she had been drinking a large amount of fluid. The urine was clear of albumin, however. She was given 50,000 I.U. of progynon intramuscularly and put on 1100 I.U. theelol per day. This was soon changed to 1 mg. of stilbestrol per day. On April 6 her weight was 196 and blood pressure 118/72. The headache had gone, but there was a 3-plus albumin in the voided urine. Twice a week for the next month she received 50,000 I.U. of progynon B in addition to her daily stilbestrol. On April 27 her blood pressure was 110/68, weight 200, and urinary output had risen to 1,600 c.c. per diem. On May 4 her pressure was 156/80, weight 200 pounds, and the urine showed a plus albumin. On May 5 a medical induction was done, followed by artificial rupture of the membranes. Two hours after labor began, she delivered a 9-pound 14-ounce normal male. One tiny white infarct was seen on the edge of the placenta on its maternal aspect. The patient had an easy convalescence. On June 17, 1939, her weight was 175 and her blood pressure 124/84.

CASE 4.—(Courtesy Dr. H. Mosser.) Mrs. T., aged 29 years, had spent three years in a sanatorium for tuberculosis during her adolescence and was still on pneumothorax therapy. She had had two boys, the younger being 6 years old. These had been normal pregnancies in each case. The menstrual history was normal. Her last menstrual period was on May 2, 1939. On Oct. 1, 1939, her weight was 132, representing a gain of 10 pounds in the pregnancy up to that time, her blood pressure was 124/82 and the urine was negative. On November 2, there was some edema of the legs and headache was severe and constant. The weight was now 142 pounds, of which 4 pounds had been gained in the previous week. The blood pressure was 126/90, and there was a trace of alubumin in the urine. An estrin test done on the blood was negative. Therefore on November 3 she was given 20,000 I.U. of progynon B intramuscularly. Her blood pressure by that time had risen to 130/96. On November 4 she reported less edema and an increased urinary output during the night. The blood pressure had fallen to 126/80. The dose of progynon B was repeated and she was put on 2 mg. of stilbestrol daily. On November 9, the weight was 140, the blood pressure 124/90, and there was a trace of albumin in the urine. On November 26, the weight was the same, the pressure 124/80, the urine showed a one-plus albumin, and the stilbestrol was therefore raised to 3 mg. per day. On January 1 there was no change. On January 18 the weight was 144, the pressure 130/90, and the edema was increased. On February 4 there was no albumin, the weight was 143, and the pressure 138/90. On February 9 at 5:00 P.M. spontaneous labor began, the blood pressure being 166/110 and the patient somewhat dull mentally. A catheter urine showed a 2-plus albumin, no casts, and 3 to 5 pus cells per high power field. She was given 50,000 I.U. of progynon B at this time. The pressure was 138/70 at 9:00 P.M. The membranes were ruptured artificially in order to expedite labor, and normal delivery occurred an hour later of a male child weighing 8 pounds 1 ounce. The post-partum course was uneventful. The pressure on the day after delivery was 140/80 and on July 20 was 126/80.

CASE 5.—Mrs. D., aged 45 years, had had no previous pregnancies here. Her last menstrual period began on July 7, 1939. She was first seen on Oct. 3, 1939, when two or more months pregnant. She had been under treatment for pernicious anemia with cord changes for the preceding fourteen months. Her weight was 130 and blood pressure 140/84 when first seen. The blood estrin was negative. By January 4 her weight had risen to 140 and blood pressure to 138/88. The urine was clear of albumin. On March 7 there was a sudden weight gain of 7 pounds to 145, and the pressure jumped to 160/94. There was a slight edema and a trace of albumin in the urine. Her blood estrin was still negative. She was put on 1 mg. of stilbestrol per day. On the fourteenth her weight was 146, pressure 148/92, the edema was unchanged, the urine clear, and she "felt wonder-

ful.'' The dosage of stilbestrol was doubled. On the twenty-third her weight had fallen to 145 and blood pressure to 144/86. There was no edema. On April 2 the pressure had jumped to 170/102, weight to 146, there was slight leg edema and a 2-plus albuminuria. Stilbestrol per day was increased to 3 mg. On the sixth her weight was 142, urine clear, pressure 164/94. She was given 50,000 I.U. of progynon B. On the ninth day her weight was 142, pressure 156/88, the albumin 2-plus, and the hypodermic of 50,000 I.U. of progynon B was repeated. There were never any headaches nor visual disturbances now or later. On the thirteenth she revealed a weight of 141, albumin one-plus, and a pressure of 156/84. She had received 20,000 I.U. of progynon B on the eleventh and this was now repeated. On the sixteenth her weight was 141, there was slight leg edema, and the pressure was 174/102. The head had been deeply fixed since March 23, and the urine showed a 2-plus albumin. The 20,000 I.U. of progynon B were repeated. On the seventeenth she had an induction with castor oil and artificial rupture of the membranes (after breaking down a conglutination of the cervical canal). Her vaginal and cervical tissues were soft and I thought she could deliver vaginally. She had hard uterine contractions all afternoon without effecting any dilatation of the cervix. Accordingly a low cesarean section was done twelve hours after the rupture of the membranes. The placenta appeared grossly normal. The uterine wall at operation bled less than at any cesarean section I have ever seen, curiously enough! The postoperative course was completely afebrile and uneventful. The male child weighed 7 pounds 4 ounces and did well. Her blood pressure on May 30, 1940, was 150/88 and she has remained well, with no exacerbation of her pernicious anemia.

CASE 6.—(Courtesy Dr. H. Mosser.) Mrs. F., aged 29 years. Her last menses had begun on Aug. 15, 1939. There was a history of short cycles with rather heavy flows at the periods. There was some nausea and vomiting in the early months of pregnancy. On Oct. 24, 1939, her weight was 134 and blood pressure 114/70. On October 30, the blood estrin was negative and urine normal. On January 12 her weight was 152 and blood pressure 126/80. The urine was negative. By February 7 her weight had increased to 159 but the urine was still normal. There was some edema of the extremities on arising each morning, however. There was the suggestion of some hydramnios. Her physician gave her wheat germ oil on the strength of the hydramnios and despite the negative blood estrin found earlier. She promptly gained 8 pounds in the next twenty days on this regime, and on February 27 her blood pressure had risen to 130/90. A blood estrin repeated on March 2 was again negative and, perhaps because no oil had been taken since February 27, her pressure had reverted to 114/70 and the urine was normal. She was put on 3 mg. of stilbestrol each day, and on March 16 her weight was 170 and pressure 126/90. The urine was normal. There was only slight ankle edema. The dose of stilbestrol was raised to 4 mg. per day and she at once reported an increased output of urine. On March 30 her weight was 170, the blood pressure was 124/84 and there was a faint trace of albumin in the urine. On April 3 the edema and albuminuria were the same, the weight was 173, and the pressure was 120/80. On May 4 there had been a transient headache, her weight was 181 pounds, and pressure 134/94. There was still a faint trace of albumin in the urine. On May 7 she spontaneously had ''show,'' with a blood pressure of 150/100, and she was sent to the hospital at 11:30 A.M. She was promptly given 50,000 I.U. of progynon B. This was repeated at 4:00 P.M. and the membranes were ruptured artificially. Labor began promptly and terminated at 11:00 P.M. in the delivery of a normal 8-pound 8-ounce male. The next day her pressure was 130/90 and she voided normally. On May 15 her pressure was 112/70. On June 22 the pressure was 120/78.

CASE 7.—(Courtesy of Dr. H. Pink.) Mrs. H., aged 39 years, had had two children. Her last menstrual date was Dec. 1, 1938. She was first seen by me on July 30, 1939, in the hospital, at which time her blood pressure was 150/88 and there was no edema, but she had had persistent headaches and visual disturbances, with a one-plus albumin in the urine. She was then 7½ months pregnant. She had a negative blood estrin, and therefore was discharged on 1 mg. of stilbestrol each day. On August 18 she was again admitted with a story of severe headaches for the previous two days, oliguria for two days, but no visual disturbance and no

edema. She had a 2-plus albuminuria and was apparently due in two weeks. She was given 50,000 I.U. of progynon B intramuscularly, as well as a sedative. Spontaneous labor with hard pains began at 4:00 A.M. on August 19. Her blood pressure then was 166/86. A 2-plus albumin (catheter samples) persisted all that day, although she received 50,000 I.U. of progynon B at 10:30 A.M. and 1:00 P.M. At 5:00 P.M. her pressure was 140/70 and her urine output was scanty with no casts, but there were a few red blood cells in it. Labor began to slow up and the head was still unengaged. At 7:00 P.M. her blood pressure jumped suddenly to 170/110 and 50,000 I.U. of progynon were repeated. Her membranes were ruptured artificially and the cervix was dilated manually from a diameter of 3 up to 5 cm. dilatation under cyclopropane. Strong pains began at once and she delivered in bed in half an hour. A normal child of 5½ pounds was born. The placenta was normal. A small post-partum hemorrhage kept up for the next three hours, at the end of which time her blood pressure had fallen to 134/38. The bleeding was then checked with ergometrine. On August 20, her blood pressure was 164/0. She had an uneventful recovery, revealing a large fibroid uterus as the puerperium passed. On August 22 her blood pressure was 154/76. Stilbestrol was continued. On the twenty-fifth her pressure was 128/78, the stilbestrol was stopped, and a moderate lactation ensued on the cessation of stilbestrol therapy. In June, 1940, her blood pressure was 120/70 and urine clear.

These protocols have been presented in great detail, with emphasis on the clinical aspects of the case histories. These were all private patients and the series is therefore uncontrolled. Most of the women were given too small doses of estrogens. Those with any experience of these cases will understand at a glance whether the therapy here described has been helpful. It should be remembered that none of these women was restricted in diet beyond decreasing salt intake in Cases 2 and 3, and there was absolutely no restriction of their usual activity in any patient but Case 2. Had bed rest been enforced generally the apparent benefits of the treatment upon blood pressures, for example, would undoubtedly have been more striking. It has seemed to me that the recovery of these women treated by estrogens has been very satisfactory. In many of them the blood pressure has reverted to normal within the first ten days post partum. That estrin can be given too late is illustrated by our fatal case (see below).

It may be objected, that the criteria I have used for the recognition of pre-eclampsia are open to criticism.[5, 6] Certainly I do not regard as "pre-eclamptic" the great majority of toxic women usually so labeled,[7] and would not expect the administration of estrogens to be helpful to all such women taken indiscriminately;[8] therefore the protocols of two classical convulsive cases are here given.

CASE 1.—(Courtesy Dr. H. Mosser.) Mrs. H., aged 19 years, primipara, menstruated last on Nov. 27, 1938. Her weight on Feb. 1, 1939, was 100 pounds, blood pressure was 124/70, and the urine was clear of albumin. On July 31 the blood pressure was 150/100, a plus albuminuria had appeared and her weight was 118. On salt restriction the albumin cleared and the pressure fell to 126/100. She felt well. On August 13, she went swimming in the lake. Next morning she suddenly developed headache and epigastric distress, as well as an oliguria which she herself noticed. Her doctor at once rushed her into the hospital where a 3-plus albuminuria was found, as well as 5 pus cells per high power field. On that day at 2:00 P.M., when I saw her first, she had headache, no visual disturbances, some liver tenderness, and was vomiting. She was mentally clear. There was no edema. There were painless uterine contractions, the head was engaging, and her blood pressure was

206/158. A blood estrin was negative. 250,000 I.U. of progynon B were promptly given at 2:30 P.M. due to an interne's mistake! (50,000 I.U. had been the dose ordered.) At that time there was the first convulsion. Seven more convulsions occurred before 10:00 P.M. Finally they became almost continuous. After 2:30 P.M. there was an increasing stupor. The urine became increasingly bloody with hyaline and granular casts, and amounted to only 30 c.c. every three hours; 50,000 I.U. of progynon B were given at 9:00 P.M. Anuria developed at 1:00 A.M. in spite of 500 c.c. of 10 per cent glucose solution given by vein at midnight. The pressure had been 146/110 most of the afternoon, but this fell to 118/78 about 1:00 A.M. The fetal heart was normal until it ceased suddenly at 2:30 A.M. when her poor pains had effected 7 cm. dilatation. She died at 3:10 A.M. The autopsy (Dr. John Fisher) revealed necrosis and many hemorrhages in the enlarged liver, nephrosis, slight ascites and pleural effusion, pulmonary edema, an extensive fresh hemorrhage throughout the pons which had broken into the fourth ventricle, subendocardial and pulmonary hemorrhages, submucous bladder hemorrhages, and a purulent bronchitis. The undelivered female fetus weighed 2,200 Gm. and appeared normal. The placenta appeared normal. Microscopic study showed peripheral necrosis of the liver lobules about the portal areas. The hemorrhages extended beyond these areas. Elsewhere the liver cells were comparatively unchanged. The tubular epithelium of the kidneys was much swollen, nearly obliterating their lumina in certain areas. Many casts of all types were seen. The glomeruli were compact and ischemic. No vascular sclerosis nor hemorrhages were seen. The corpus luteum definitely was degenerating. In the pituitary the chromophil cells were unusually prominent and some of the eosinophilic cells were small and poorly defined. No definite necroses nor degeneration could be found there however.

CASE 2.—(Courtesy Dr. J. F. Simpson.) Mrs. A., aged 25 years, primipara. Her last menses began Oct. 3, 1938. I first saw her on July 5, 1939, at which time her blood pressure was 140/88, her urine solid with albumin, and she had become quite deaf. Her blood estrin was positive. A medical induction was advised and failed. On July 12 she was admitted to the hospital with the same degree of albuminuria, a marked oliguria, and a blood pressure of 140/108. She was dull and apathetic. Her blood estrin had become negative. There was no headache. Her edema markedly increased during the day. At noon her membranes were artificially ruptured. She soon went into labor, had one convulsion just after midnight and the child's scalp showed at 1:00 A.M. 50,000 I.U. of progynon B were promptly given. Manual rotation and forceps delivery of a persistent occipitoposterior were performed under ether anesthesia. A normal female child weighing 6 pounds 15 ounces was delivered, and a retention catheter was inserted. The placenta was quite normal in appearance. A moderate post-partum hemorrhage occurred. She became conscious at 3:30 A.M. and the progynon B was repeated at 5:00 A.M. but she was still slightly drowsy at 7:30 A.M. There was no urine output until 11:00 A.M. At 1:00 P.M. there was a 3-plus albumin. Up to 3:00 P.M. she had excreted 5 ounces and the progynon B was then repeated. At 5:00 P.M. there was only a trace of albumin in the urine!! In the first twenty-four hours after her delivery she voided 34 ounces of urine and also wet her bed, although her intake was but 24 ounces. On the thirteenth her pressure was 136/100, urine was clear, and the edema was rapidly disappearing, but a severe occipital headache lasted for the first three days of the puerperium. Her last progynon B was given on that day. By July 17 she appeared well but had a pressure of 138/96. She has been well since, but I have no later blood pressure or urine reports.

It will appear from the foregoing that the estrogens have an important place in the management of true pre-eclampsia and eclampsia. They are especially useful in maintaining urine output, decreasing albuminuria, and relieving the stupor, headache, and visual disturbances preceding and accompanying convulsions.

BARRIE'S OBSERVATIONS*

If low blood estrogen values play a vital role in the onset of eclampsia an antiestrogen such as vitamin E[9] if given by mistake to a pre-eclamptic could be expected to depress these values still further and precipitate convulsions. One of my colleagues and I have had experiences suggesting that such was possible, as Case 6 might indicate, for example. Barrie[10] has recently obtained some interesting data on animals to support such an opinion. I am permitted to quote her letter, now a year old, giving her preliminary observations in extenso:

"In 1939 (J. Obst. & Gynaec. Brit. Emp. **46**: 49, 1939) an account was given of a number of cases of toxemia occurring in rats fed on a diet partially deficient in vitamin E. The pathologic changes included fatty infiltration of the liver, deposition of calcium salts in the kidneys, which also showed large amounts of albumin, and associated degeneration of the tubule cells. A number of cases have been observed in which the animals developed convulsions shortly before death. The following examples illustrate the conditions:

"Rat A was 4 months old and had been fed on a vitamin E-free diet from weaning. It was mated and given one very large dose of 2.5 mg. of d-l-a tocopherol (vitamin E) on the same day. On the eighteenth day of pregnancy the animal was extremely ill and there was blood on the fur around the mouth; on the following day it was having fits of violent convulsions; the head was drawn over to one side and then the rat turned over and over and stiffened its legs in a violent spasm which relaxed leaving the animal limp but with the head still drawn to one side. The rat was killed on the following day and 9 living fetuses were found in utero.

"Rat B was of the same age and had received the same diet and the same treatment. The convulsions occurred at intervals for 6 days preceding the birth of a live litter of 7. The head rocked backwards and forwards and the eyes rolled; the tail stiffened, then the body was drawn stiffly into a ball and thrown into the air several times with the violence of the convulsions.

"These observations can only be regarded as preliminary; there were about 20 such cases. No figure can yet be given for the frequency of occurrence among toxic rats and no adequate data relating the condition with dosage of vitamin E. Both the rats described were sterile before treatment and both received sufficient vitamin E on mating to produce a viable litter. I offer no explanation of the condition, but record it in view of the possibility that it may be in some way analogous to eclampsia in man."

DISCUSSION

I am aware that Young, Obata, and Oden[11] have produced convulsive deaths in laboratory animals by injections of placental extracts, Young and Obata claiming that the animals at autopsy showed eclamptic lesions. Oden was unable to confirm this histologic observation, however. Dieckmann[12] has reproduced in dogs the hepatic lesion described for eclampsia by means of intravenous injections of tissue fibrinogen, but his animals did not have convulsions. It appears that Barrie is the first one to reproduce in an animal both the convulsive signs of eclampsia and similar histologic characters by means of a dietary factor administered orally.

In my two cases already published, the woman were undelivered when first seen, but labor supervened rather easily several hours after the exhibition of the estrogen. There was no evidence of a change in the estrogens in the blood for at least seven hours after estrin had been

*To be published in detail in a later paper.

given intramuscularly, but thereafter there were no convulsions, the stupor rapidly diminished, there was no important change in blood pressure, and the urinary albumin disappeared rapidly—in the post-partum case this was complete in eleven hours after being maximally heavy at delivery! There was continued excretion of urine and never complete oliguria. The dosage to be advised was uncertain from that experience, however.

Further use of this treatment has convinced me that it needs to be supplemented in the convulsing cases, but only in them, with sedatives such as morphia during at least the first seven hours after estrin has been given. But thereafter, if large enough doses of the latter have been used, the convulsive tendency ceases, stupor disappears gradually, the kidneys do not close down and may actually, as in one of our severe pre-eclamptics, show a decreasing albuminuria and excretion of less blood and casts even while the blood pressure is rising slightly. Labor can be induced readily by rupture of the membranes, at least in women in the last month of pregnancy, the pains are unusually effective, and may continue even when the woman is becoming moribund from intracranial hemorrhage, as in our fatal case. The course of these patients is unlike that of eclamptic patients treated with sedatives but without estrin, and in order to demonstrate this beyond cavil, our second convulsive case in this report received nothing but estrin. Obviously, the greatest flaw in the work is that it is a small and uncontrolled series. However, control was impossible as these were all either private patients or patients seen in consultation. The use of controls in such work raises a delicate ethical problem.

It is of interest that the fatal convulsive case did not show any change in her blood estrogen although the interne gave her 250,000 I.U. of progynon B by mistake!

A report in the literature[13] suggesting that the use of an estrogen actually may precipitate eclamptic convulsions ignores the fact that the convulsions mentioned there came on long after the estrogen had been given (over twenty-one hours). My experience leads me to suspect that more estrin, rather than less, was demanded by the patient's condition.

SUMMARY

1. As an addition to the records of the pre-eclamptic and two eclamptic women treated by estrogens previously reported by me, the protocols of 7 more pre-eclamptic and 2 convulsive eclamptic patients similarly treated are given here.

2. These women were not restricted as regards activity or diet except for limitation of sodium chloride in several of them.

3. Barrie, working in England, has recorded eclamptic-like convulsions in certain E-defective rats suddenly given large doses of d-l-a tocopherol. The histologic lesions in these animals simulated those of human eclampsia. I relate this to the theory that estrogen defect is an important factor in the onset of eclampsia, as vitamin E is antiestrogenic in character.

4. The clinical effects of estrogens on these women are slow in developing, but favorable influences on convulsions, stupor, blood pressure, urinary volume, and albumin have been observed.

I desire to thank Schering (Canada) Limited for the progynon B used in these studies.

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THE RESULTS IN TREATMENT OF 600 INCOMPLETE ABORTIONS

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Approximately 150 patients, or 17 per cent, of the total admissions to the Gynecological Service of the Queens General Hospital, are admitted each year with the diagnosis of incomplete abortion, infected or otherwise. This is exclusive of those patients more than four and one-half months' gravid who are placed under the supervision of the Obstetrical Service.

A survey of the case records of 600 abortions on the Gynecological Service, from 1935 to 1940, is presented in this paper. Although therapy for the greater number was conservative, some patients were treated radically with less favorable results. In determining the proper therapy, the necessity of understanding thoroughly the pathology of this disease and its relationship to the bacteriologic findings cannot be overemphasized.

On admission to the hospital, the patient is tentatively classified in one of the following four groups:

I. *Incomplete Abortion, Afebrile.*—The temperature must be below 100.4°F., and there must be no history of induction or of chills or fever.

II. *Potentially Infected Abortion.*—The patient is afebrile on admission, but has a history of chills or fever, or of criminal interference.

III. *Infected Abortion.*—The temperature is at least 100.4°F., and there is no clinical evidence of extrauterine infection.

IV. *Septic Abortion.*—The patient is considered septic if signs point to an extension of the infection beyond the uterus, or if the blood culture is positive.

RESULTS IN GROUP I ABORTIONS

There were 423 patients who were afebrile on admission and gave no history of interference. Of these, 221 were curetted after being observed for forty-eight hours or more in the hospital. In the remainder of patients, the abortion was either completed spontaneously or by the removal of tissue lying free in the cervical canal. There were no deaths in the entire group.

Our results demonstrated that, although 40 per cent of our patients did not require curettage, their average hospital stay was seven days as compared to the five-day average for those patients who were curetted.

Hemorrhage rarely requires immediate curettage since, in almost all instances of severe bleeding, the cause is placental tissue in the cervical canal. Severe bleeding can be controlled by its removal merely with the ovum forceps.

We cannot overemphasize the necessity for waiting forty-eight hours before curetting any incomplete abortion for the following reasons:

1. Further information is often obtained from patients who, on admission, denied manipulation.

2. A normal temperature on admission may be the bottom of a spiking temperature that may become apparent the following day.

3. The vaginal examination on admission does not always reveal the presence of an extrauterine infection. An illustrative case is that of a patient who, on vaginal examination at the time of her entrance to the hospital, revealed no signs of extrauterine infection although the patient admitted recent criminal interference. On the next day, signs of a fulminating peritonitis were present. She died on the third day. We may assume that the infection had already spread beyond the uterine cavity when the patient was first examined, although time was necessary for this to be clinically evident.

RESULTS IN GROUP II ABORTIONS

There were 31 patients who were afebrile on admission, of whom 24 entered with a history of some form of mechanical interference with their pregnancy, and only 7 with chills or fever prior to entering the hospital. Twenty-nine of these patients remained afebrile, whereas 2 had a mild febrile course. Sixteen were curetted after five days of normal temperature with no resultant morbidity. There were no mortalities.

We have selected an arbitrary period of five days before curettage in this group because longer observation is warranted in a potentially infected case. Whatever minor infection that may have been present would have subsided, and sufficient immune bodies formed to prevent spread of any persistent infection following manipulation.

RESULTS IN GROUP III ABORTIONS

There were 117 cases on admission where the infection was limited to the uterus. All patients received supportive therapy, and one-fourth were given sulfanilamide in addition. Forty-five patients were curetted. Twenty-nine were curetted after being afebrile for more than five days, with a postoperative morbidity of 3.4 per cent. Of the remaining 16,

3 were curetted while mildly febrile, and 13 were curetted after an afebrile period of less than five days, with a gross morbidity of 50 per cent. There was 1 death in the entire group.

It is in the treatment of cases in Group III where the infection is presumably limited to the uterus that there is a major difference of opinion between schools of gynecology. Studdiford,[1] representing one group, favors immediate curettage of all Group III cases when the offending organism is not the *Streptococcus hemolyticus*. We share the opinion of the other school which employs conservative therapy because of the following:

1. The uterine culture taken on admission does not always reveal the true invading organism. We have observed on several occasions that a nonpathogenic or negative culture was obtained on admission, whereas pure cultures of *Streptococcus hemolyticus* were later isolated. This phenomenon may be explained by the invasion of the uterine wall by a minimal group of virulent hemolytic streptococci with insufficient numbers in the uterine cavity to give a positive culture.

2. As mentioned above, one cannot exclude by vaginal examination the presence of extrauterine infection.

3. We have had no deaths with conservative treatment of Group III cases. In our single death in this group, Case 40311, the patient was afebrile on admission and denied interference with her pregnancy. On the second day the temperature was 102°F. On vaginal examination there was no evidence of any extrauterine infection. Necrotic tissue was removed from the uterus with a sponge forceps. The temperature rose to 104°F. on the third and fourth days, and the patient died on the fifth day. Post-mortem examination revealed the presence of a diffuse peritonitis, acute suppurative endometritis and myometritis, thrombophlebitis of the broad ligament, and multiple abscesses of the lung. Blood and uterine cultures taken at autopsy were reported as *Streptococcus hemolyticus*. Sulfanilamide was not available. Apparently the patient had an extremely virulent type of infection which might not have responded to any form of therapy. It is conjectural as to what the effect of sulfanilamide might have been. The radical treatment of this case by the early invasion of the uterus with the ovum forceps might have been responsible for the rapid dissemination of the organism.

SULFANILAMIDE THERAPY

We have found sulfanilamide to be invaluable in the treatment of febrile abortions. Although we have only given the drug to 25 per cent of our Group III and 65 per cent of Group IV patients, it is our belief that all febrile abortions warrant sulfanilamide on admission. Our reasons are:

1. The identification of the organism from the uterine culture cannot be obtained in less than twelve to twenty-four hours. This would delay the early administration of the drug.

2. As before mentioned, the initial uterine culture may not indicate the true invading organism.

3. As soon as toxic manifestations appear, the drug can be withdrawn without serious damage to the patient.

Our mode of administration of sulfanilamide has been in the form of prontylin, neoprontosil, or prontosil. The dosage for prontylin was ¾ gr., for prontosil 1.5 c.c., and for neoprontosil 1 c.c., per pound of body weight in 4 divided doses for the first twenty-four hours. Whenever

possible, prontylin was the drug of choice, and this was administered with equal doses of sodium bicarbonate. Subsequent dosage depended upon the clinical course and the offending organism.

A. *Streptococcus Hemolyticus Infections.*—The total dose is repeated for the second day, three-fourths the dose for two days, and one-half the total dose thereafter. This amount is gradually reduced with clinical improvement of the patient.

B. *Infections Other Than Streptococcus Hemolyticus.*—A similar dosage is given. However, if the fever persists by the end of the first week, the uterine cultures should be repeated, and if hemolytic streptococci are not isolated at this time, the use of the drug is discontinued.

After the blood volume has been restored by transfusion and infusions, the total twenty-four-hour fluid intake is limited to 2,000 c.c. Complete blood counts are done before the drug is administered, and for the first three days, the fifth, and the seventh day, and twice weekly thereafter. The urine is examined daily for bile, albumin, and red blood cells. Blood chemistry determinations for nonprotein nitrogen, chloride, and carbon dioxide combining power are obtained when there is any question of renal impairment or acidosis. Blood titers for sulfanilamide were not determined routinely.

It is known[2] that not all strains of the *Streptococcus hemolyticus* are equally susceptible to the action of sulfanilamide, and that the infection is mild when the organism is not of the invasive strain. Furthermore, it was frequently noted that the high fever in Group III patients who had not received sulfanilamide would subside following spontaneous evacuation of placental tissue. If sulfanilamide had been given to these patients and one were hasty in his conclusions, further cures for the drug would have been recorded. Therefore, to determine its therapeutic value, results only for Group IV patients were considered.

RESULTS IN GROUP IV ABORTIONS

There were 29 patients who, on admission to the hospital, showed signs of extension of infection beyond the uterus. Of these, 20 survived and 9 died. Seventeen patients received sulfanilamide. Only 2 patients were curetted after a long afebrile period, and 3 required surgical drainage of pelvic abscesses with recovery.

In an analysis of the fatalities in this group, we would like to first summarize those cases which were probably hopeless on admission to the hospital.

The patient in Case 27408 entered the hospital with a history of previous manipulation, and a temperature of 100.4°F. In twenty-four hours there were clinical signs of a fulminating peritonitis, and the patient died on the third day. The post-mortem findings were: generalized peritonitis and septic embolic abscesses in the kidney and myocardium. Post-mortem cultures were reported as *Staphylococcus aureus hemolyticus.*

The patient in Case 16109 entered the hospital with a temperature of 104.4° F. *B. welchii* were isolated from the uterus and blood stream and, although the patient received specific antitoxin, she died on the fifth day. On post-mortem examination, a perforated uterus and peritonitis were found.

The patient in Case 56550 died after a febrile course of seventeen days. The post-mortem findings were: perforated uterus and generalized peritonitis. The cultures taken at autopsy were reported positive for *Staphylococcus aureus hemolyticus*. Sulfanilamide was administered.

Of the remaining 6 fatalities, the following 3 patients were treated at a time when sulfanilamide was not available. Two of these died of *Streptococcus hemolyticus* infections.

The patient in Case 10691 confessed to the insertion of a catheter several days before entering the hospital. The temperature was elevated for four days and then normal until she was discharged from the hospital on the thirteenth day. She was re-admitted eight days later after the re-insertion of a catheter. The temperature was normal on her second admission, and continued so for two days. A tender ovary was palpated. Cultures were not taken. A curettage was performed on the third day while the patient was afebrile. Following the procedure, the temperature rose to 102.6°F. The course of her disease was septic for twenty-four days when she died. Hemolytic streptococci were isolated from the blood stream during her illness. Post-mortem findings were: thrombophlebitis of the broad ligament, acute mitral and aortic endocarditis, and miliary abscesses of the myocardium. Even the more radical investigators do not favor curettage in the presence of extrauterine spread of an infection. In this case, the operator ignored the finding of a tender ovary and curetted the uterus.

The patient in Case 57204 entered the hospital with a temperature of 100.4°F. She denied interference with her pregnancy. Placental tissue present in the cervical canal was removed with the sponge forceps. On the second day, clinical signs of peritonitis were present and she died on the third day. On post-mortem examination, generalized peritonitis, septic endometritis, and an ovarian abscess were found. *Streptococcus hemolyticus* was isolated from the uterus. No cultures were taken before death.

Case 9745 denied interference with her pregnancy. The temperature on admission was 104° F. *Streptococcus hemolyticus* was isolated from the blood stream. The course of the disease was septic for seventeen days when she died. The post-mortem findings were: septic endometritis and thrombophlebitis, septic endocarditis, brain abscess and panophthalmia. The cultures taken at autopsy were reported as *Streptococcus hemolyticus*.

The following 3 fatal cases received sulfanilamide therapy.

The patient in Case 88486 was admitted with a temperature of 104.4°F. Streptococcus hemolyticus was isolated from the uterus and blood stream. On the second day, physical signs of acute bacterial endocarditis were present. After forty-eight hours of sulfanilamide therapy, the drug was discontinued because of a marked leucopenia. The patient died four days later. Post-mortem findings were: endometritis and acute bacterial endocarditis.

The patient in Case 84718 had a septic abortion induced by a "slippery elm." The temperature on admission was 103.4° F. Nonhemolytic streptococci were isolated from the uterus, whereas repeated blood cultures were sterile. The patient had a bilateral parametritis. On the fifth day the temperature rose to 106° F., and the course of her disease was septic for thirty-four days when she died. The post-mortem findings were: acute endometritis, thrombophlebitis of the broad ligament, septic pulmonary infarct, and generalized peritonitis. Hemolytic streptococci, however, were isolated from the post-mortem cultures. The patient received neoprontosil on the fifth day, and the routine dosage was continued for five days. At this time, jaundice and a leucopenia appeared, and the drug was discontinued. The white blood count returned to normal in two days, whereas the jaundice persisted for sixteen days. The patient died on the thirty-fourth day after admission. This case demonstrates that the initial uterine culture may not reveal the true invading organism.

The patient in Case 97236 had a septic abortion induced by a catheter. Her temperature was 104°F. on admission. The abortion was complicated by a parametritis. *B. coli* were isolated from the uterus and blood stream. Sulfanilamide was administered. The course of her disease was septic for twenty-five days when she died. The post-mortem findings were: septic endometritis, left tubo-ovarian abscess, left parametritis, left pelvic cellulitis, left pelvic abscess, recto-sigmoid abscess, and generalized peritonitis. Cultures taken at autopsy were reported as *B. coli.*

Of 21 patients in Group IV who received sulfanilamide therapy, 4 died. However, in reviewing these mortalities, described in detail above, we find that only 2 patients had *Streptococcus hemolyticus* infections. One, who showed clinical evidence of an acute bacterial endocarditis on the second day and died on the fifth day, was probably too far advanced for an adequate test of sulfanilamide. Unfortunately, the second patient developed a leucopenia and jaundice, forcing us to discontinue the drug after only five days of treatment.

On the other hand, we have had 3 patients with pelvic peritonitis due to the *Streptococcus hemolyticus* who recovered under sulfanilamide therapy. Hitherto, these cases were considered hopeless.

The patient in Case 91199 was admitted with the diagnosis of parametritis and pelvic peritonitis. Hemolytic streptococci were isolated from the uterus and blood stream. Ochsner regime was instituted and, in addition, she received neoprontosil and repeated small blood transfusions. The temperature subsided by lysis at the end of the ninth day of hospitalization.

The patients in Cases 99367 and 85650 had positive uterine cultures for *Streptococcus hemolyticus,* whereas the blood cultures were sterile. Routine treatment was administered. The former was febrile for eight days, and the latter for six days.

Case 78992 entered the hospital with a parametritis and positive blood and uterine *Streptococcus hemolyticus* cultures. Under prontylin therapy, she became afebrile in five days.

Two patients were admitted with parametritis and had positive *Streptococcus hemolyticus* cultures only of the uterus. Under prontylin therapy, 1 was febrile for thirty-five days and the other for six days.

There were 7 patients with parametritis, of whom 4 were due to the *Streptococcus hemolyticus,* 1 to the *Streptococcus nonhemolyticus* and *B. coli,* 1 to a *Streptococcus viridans* and *B. coli,* and 1 to a *Streptococcus viridans.* None of these had a positive blood culture. All received sulfanilamide; however, their average morbidity was nineteen days as compared to eleven days in the above similarly treated *Streptococcus hemolyticus* group.

There were no deaths attributed to sulfanilamide, although we had to discontinue the drug in 7 patients (out of 17) in Group IV because of toxic manifestations. These included 2 patients with jaundice and leucopenia, 2 with leucopenia, 1 with leucopenia and a persistence of fever, and another with a persistent diarrhea. The frequency of toxic symptoms in this group can be attributed to the relatively large dosage of the drug given.

DISCUSSION

We have had good results with the conservative treatment of abortions where the infection is apparently limited to the uterus. The only patient of this group who died received radical therapy.

It is generally agreed that patients with an extrauterine infection should be treated conservatively. The only recent addition to our armamentarium is sulfanilamide. In the *Streptococcus hemolyticus* type of infected abortion, we have found the drug reduces the morbidity and has saved some of the hitherto hopeless cases.

Because we believe in the conservative treatment of both potentially and actually infected abortions of all types, it would seem advantageous to avoid even the slightest manipulation that might spread infection. On numerous occasions we have observed that the digital vaginal examination caused exacerbations in infected abortions. This procedure should be reserved only for cases of questionable diagnosis, or where immediate surgical intervention for localized pus is contemplated. Otherwise, the patient should be examined only after a five-day afebrile period. This, of necessity, would prevent an adequate pathologic classification of the infected case on admission; a point which we feel of no therapeutic moment.

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LEAD MOBILIZATION ACCOMPANYING TOXEMIA OF PREGNANCY

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IN THE course of a survey of lead concentration in tissue in disease, high values were found in kidney and pituitary of three women dying of toxemia of pregnancy. In these cases the fetal tissues also showed increased lead concentration. As a result of these findings, estimations of the lead content of blood and urine have been made on 18 patients with a clinical diagnosis of toxemia of pregnancy. This included 12 cases of pre-eclampsia, 1 case of eclampsia, 3 cases of nephritic toxemia and 2 of essential hypertension. Fifteen normally pregnant women in the same age group, and of similar economic status served as controls.

The salient studies in both groups are shown in Tables I and II. In patients with toxemia, the mean concentration of lead in whole blood was 0.053 mg. per 100 c.c. (±0.0070 S.E.). This is well above the average established for normals by the method employed.[1] By this method, blood lead values for normal individuals average 0.0295 mg. per 100 c.c. (±0.0029 S.E.) and findings of 0.060 or higher are considered indicative of excessive absorption or of lead mobilization. Eight toxemic patients showed blood lead concentrations above the range of normal established by Letonoff and Reinhold;[1] and by comparison with the control group, six presented significantly elevated values. Excretion of lead in the urine was measured in 3 of the cases of toxemia of pregnancy and was found to exceed normal limits in all cases. In 2 cases, this was associated with elevated blood lead; in the third, the blood lead value was normal.

TABLE I. TOXEMIA

NO.	PATIENT	DATE 1940	AGE	COLOR	MONTHS PREGNANT	EDEMA	BLOOD PRESSURE	KAHN	SERUM		PLASMA CO_2 VOL. %
									PROTEIN GM. %	NaCl MG. %	
1	J. S.	1-10	28	B	7	+	198/106	++++	6.7	580	34
2	R. W.	1- 3	38	B	9	++	170/120	Neg.	4.6	610	--
3	E. C.	2- 7	29	B	9	+	160/110	++++	6.9	---	49
4	C. M.	2- 2	23	W	9	+	175/110	Neg.	6.0	643	43
5	M. B.	2-22	23	B	8	++	150/110	Neg.	6.4	---	41
6	C. W.	2- 1	24	B	9	+++	-------	Neg.	4.8	620	40
7	J. B.	2- 2	24	B	8½	++++	100/108	Neg.	6.7	620	33
8	C. M.	3- 7	32	B	8	+++	170/110	Neg.	4.6	620	37
9	M. M.	3- 7	15	B	8	++	200/130	Neg.	5.1	652	38
10	G. M.	5- 2	39	B	6	+	150/110	+++	6.1	---	33
11	A. B.	2-28	23	B	9	+	150/110	Neg.	5.6	565	34
12	J. R.	1-20	37	B	7	?	255/120	Neg.	--	---	--
13	R. L.	1-19	28	W	9	++++	155/110	Neg.	6.2	640	31
14	E. C.	1- 4	32	B	6	+	170/120	Neg.	6.7	---	--
15	C. W.	12-27 (1939)	38	B	9	++++	170/110	++++	--	---	36
16	C. S.	2- 7	24	B	7	+	175/110	Neg.	6.0	643	43
17	W. L.	3- 7	16	B	8	?	175/115	Neg.	7.1	610	34
18	S. C.	4-21	32	W	7	+	200/120	Neg.	4.5	---	53

*Died.
†Delivered stillborn. Placenta retained. Died of peritonitis.

In the control group of 15 normal pregnant women, the average blood lead concentration of 0.031 mg. per 100 c.c. (±0.0046 S.E.) agrees closely with the average normal value for both sexes from the general population. Individual values fall within normal limits with one exception. This patient was a gypsy admitted just before delivery with an incomplete and unsatisfactory history. Clinically she presented no evidence of toxemia.

Comparison of the mean values for blood lead in the toxemic and control groups by the method described by Student, using Fisher's[2] Table of t indicated that the difference is not due to chance. Failure to elicit history of unusual exposure strongly suggests that the source of the increased blood lead is from stores accumulated through casual daily contact and activated by metabolic disturbances arising during the course of pregnancy toxemia. This hypothesis is strengthened by the observation that in two patients (1 and 7), as well as in other toxemic cases not included in this series, elevated blood lead dropped to normal limits after delivery.

OF PREGNANCY

BLOOD HB. GM. %	SUGAR	BLOOD MG. %			URINE			HISTORY	DIAGNOSIS
		UREA N	URIC ACID	LEAD	LEAD MG. 24 HR.	ALB.	CASTS, ETC.		
11	89	9	8.6	0.085	----	+++	R.B.C. Leuc.	Malaise, headache, convulsions*	Eclampsia
15.2	72	8	5.0	0.002	----	++++	Granular	0	Pre-eclampsia
9.6	54	10	5.0	0.011	----	trace	--------	0	Pre-eclampsia
10.0	87	9	5.3	0.038	----	+++	--------	Edema, vomiting	Pre-eclampsia
10.4	70	10	4.0	0.040	----	+ to ++++	--------	Spots before eyes	Pre-eclampsia
8.5	77	11	5.0	0.043	----	++++ to trace	--------	0	Pre-eclampsia
11.5	68	16	5.5	0.044	----	+++	--------	Headaches	Pre-eclampsia
8.1	77	9	2.6	0.054	----	++	--------	Headaches	Pre-eclampsia
9.6	56	10	4.3	0.062	----	++	R.B.C.	Spots before eyes, headaches	Pre-eclampsia
10.4	123	17	--	0.070		+++	Leuc. epith.	Dyspnea. 2 prev. stillbirths. Eye grounds neg.	Pre-eclampsia
8.1	70	16	4.0	0.075	----	trace		Spots before eyes	Pre-eclampsia
---	84	9	3.8	0.079	0.15	+++	R.B.C. Leuc.	Spots before eyes. Headache and vertigo	Pre-eclampsia
10.8	100	8	3.8	0.109	----	++	--------	0	Pre-eclampsia
10.0	72	8	3.6	0.064	0.189	0	0	0	*Essential Hypertension*
---	72	8	--	0.025	0.455	++++	--------	0	*Essential Hypertension*
---	87	20-10	3.8	0.001	----	++ to +++	Leuc.	0	Nephritis?
12.4	70	8	4.0	0.039	----	+	--------	0	Nephritis?
14.0	84	35	--	0.115	----	++++	Leuc.	Diarrhea, headache, albuminuric retinitis with hypertensive changes. Gen. peritonitis†	Chronic pyelonephritis. Nephrolithiasis. Cholelithiasis.

However, it appears improbable that mobilization of lead is a causative or even a contributing factor in all cases of toxemia of pregnancy. Many patients in our series with typical clinical pictures of toxemia showed normal blood lead values. It is possible that the pregnancy toxemia itself, because of its complex nature and diverse etiology, may alter factors controlling lead absorption and mobilization. It is of considerable importance, however, that in this series one-third of the patients with toxemia of pregnancy showed blood lead concentrations as great as those encountered in moderately severe lead intoxication.

As Aub and his associates[3] have previously shown for lead intoxication in general, we have noted a relationship in toxemia of pregnancy between concentration of blood lead and acidosis as measured by plasma carbon dioxide combining power (Table I). In most cases in our series the values for carbon dioxide combining power are lower than those given for normal pregnancy,[4] and the high blood lead concentrations are, in general, associated with the lower values for carbon dioxide combining power. Such degree of acidosis alone can scarcely be con-

sidered responsible for lead mobilization in pregnancy toxemias, since, in our experience, diabetic acidosis of comparable severity is infrequently associated with elevated blood lead concentrations.

The heavy drain on maternal calcium stores which normally occurs during the late months of pregnancy[5-7] may act as an additional factor, simultaneously liberating lead stored in the skeleton. In toxemia of pregnancy in particular, the combined effects of decalcification and acidosis would exert a powerful action toward mobilization of the lead stores of the body.

While it is highly possible that other factors are concerned in the increase of blood lead in toxemia of pregnancy we have been unable to establish any such relationship in our studies. In particular, no association could be demonstrated between blood pressure, edema, gain in weight, serum protein, serum chloride or uric acid, blood sugar, blood urea nitrogen, hemoglobin or urinary changes, and the blood lead concentration (Table I).

TABLE II. NORMAL PREGNANCY

NO.	PATIENT	DATE	AGE	COLOR	URINE		BLOOD PRESSURE	BLOOD LEAD
					ALB.	CASTS		
		1940						
1	L. C.	2- 4	23	B	+	0	114/70	0.011
2	B. R.	2- 1	40	W	0	0	140/88	0.011
3	F. J.	1-28	18	B	0	0	122/75	0.013
4	L. S.	2- 1	21	B	+	0	140/95	0.015
5	R. N.	2- 3	26	B	0	0	140/100	0.020
6	H. H.	1-25	17	B	+	0	124/78	0.025
7	H. R.	1- 7	25	W	++	0	110/90	0.025
8	E. W.	2-15	25	B	0	0	112/78	0.034
9	V. T.	4- 4	19	B	0	Leuc.	100/60	0.036
10	E. Ma.	2-20	15	B	0	0	115/85	0.045
11	J. L.	2- 9	37	B	++++*		120/70	0.048
12	H. B.	1-23	40	W	0	0	140/90	0.056
13	M. C.	1-26	19	W	0	0	130/78	0.077
14	B. C.	4- 4	19	B	0	Epith.	135/90	0.025
15	E. Wm.	3-23	21	B	0	Leuc. ++	180/120	0.032

*After delivery.

In evaluating the significance of increased blood lead concentrations in toxemia of pregnancy, it should be emphasized that many of the symptoms characteristic of this condition, namely, hypertension, convulsions, headache, renal changes and visual disturbances, are also prominent manifestations of lead intoxication.

Hausmann and Perry[8] have recently reported evidence of lead intoxication in a pregnant woman, associated with abnormal lead concentrations in the fetal tissues. Oliver[9] and more recently Porritt[10] and Milligan[11] have cited the greater prevalence of miscarriage and other complications of pregnancy among lead workers and in districts of the United Kingdom where drinking water contains lead in appreciable amounts. The susceptibility of the natives of the tropics to eclampsia after adopting the customs and dietary of the whites as reported by Peckham[12] suggests some relationship between eclampsia and the increased lead intake associated with civilization.

While the significance of lead in the toxemia syndrome remains to be evaluated,* it seems not unlikely, in view of the toxic manifestations accompanying elevated blood lead in lead poisoning, that comparable blood lead values, resulting from mobilized lead, contribute to the symptom complex of toxemia in pregnancy. For this reason, we believe it is important to direct the attention of those engaged in study or treatment of the toxemias of pregnancy to the fact that such conditions are often associated with mobilization of lead.

SUMMARY

Toxemia of pregnancy is frequently accompanied by mobilization of lead as indicated by quantitative blood and urine lead determinations. Evidence suggesting that lead may be a causative or contributing factor in some cases of toxemia of pregnancy has been presented.

We acknowledge our indebtedness to Drs. Catherine Macfarlane and Philip F. Williams and their associates of the Department of Obstetrics for clinical data and for permission to report these findings.

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Available data are not sufficient to allow a definite and final conclusion as to the exact time of the operation of the factor or factors which lead to the production of mongolism. On the basis of data on 58 cases of mongolism in dizygotic twins, the writer concludes that the causes of mongolism must reside in some factor or factors that cannot at any stage of development act directly on more than one ovum, zygote, or embryo. Since at all stages two or more ova, zygotes, or embryos may occur in exactly the same external environment, it is obvious that the condition can develop only from within the gametes, and so must be either chromosomal or cytoplasmic. The rarity with which two or more persons with the condition appear in one family makes it justifiable to conclude that mongolism is not produced by hereditary factors. The factors, therefore, are not considered to act at the time of the formation of the gametic chromosomes. The production of mongolism may be definitely associated with substances liberated from the ovum and from the spermatozoon, and mongolism may be the result of fertilization in which one or the other gamete was in an aged condition transitional to the nonfunctional or inactivable state. That the spermatozoa may thus be effective is shown by the abnormal sex ratio that occurs among those with mongolism. That the ovum may be similarly effective is shown by the definite relation between the mother's age and the frequency of production of mongolism. This study is based on records of 259 persons with mongolism.

J. P. Greenhill.

*Work along these lines is in progress in this laboratory.

PROTHROMBIN CONCENTRATION IN PARTURIENT WOMEN AND THEIR NEWBORN INFANTS*

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PROTHROMBIN determinations have become increasingly important in the medical management of surgical conditions, and more recently in the field of obstetrics and pediatrics, particularly in regard to hemorrhagic disease of the newborn. The original method of Howell for the determination of prothrombin using oxalated plasma and an excess of calcium has been improved upon by Quick, who uses an excess of calcium and thromboplastin. The titration method of Warner, Brinkhous, and Smith utilizes two steps; oxalated plasma freed of fibrinogen is diluted and prothrombin is converted to thrombin by the addition of thromboplastin; fibrinogen is then added, and the concentration of prothrombin is calculated and expressed in units or in percentage of normal. This method is far more accurate than the other two and has been used in the present study.

Having a satisfactory test at their disposal, Brinkhous, Smith, and Warner investigated the plasma prothrombin of infants. In a case of hemorrhagic disease, they found a value of 5 per cent on the seventh day of life. They studied the cord blood of 8 normal infants, and found values ranging from 14 to 39 per cent (average 26 per cent). Owen and co-workers using their method reported a further decrease in the amounts of prothrombin in the second to sixth days of life, when clinical bleeding is prevalent in cases of hemorrhagic disease. On the other hand, Quick, using blood from the internal jugular vein shortly after birth, found the prothrombin concentration to be nearly normal with his test, but observed a decline in the first days of life which had been shown earlier (1921) by Lucas. Owen and co-workers have shown that infants with low prothrombin values as determined by the Warner, Brinkhous, and Smith test, may have a normal prothrombin time according to the Quick test. They postulated that the quality of prothrombin may be a factor causing the discrepancy between the tests. In this way there may be compensation for the prothrombin deficiency at birth, by an increase in the speed of conversion of prothrombin to thrombin.

PRESENT STUDY

The prothrombin content of blood plasma was determined by the method of Warner, Brinkhous, and Smith, and the results expressed in percentage of normal adult controls. Twenty normal healthy pregnant women at term (during the winter of 1938 and 1939) were selected, and blood was obtained from the antecubital vein at the time of delivery, and from the fetal vessels of the placenta. In each instance, 4.5 c.c. of blood were placed into 0.5 c.c. of a 1.5 per cent solution of sodium oxalate. A second sample of blood was taken from the placenta for the

*This study was carried out under a grant from the John and Mary R. Markle Foundation.

determination of red cell count, hemoglobin, volume of packed cells, and the icteric index. The cell volume of the mothers had been determined on admission to the delivery floor.

TABLE I. PROTHROMBIN IN 20 NEWBORN INFANTS AND THEIR MOTHERS AT DELIVERY

(Titration Technique)

CASE	PER CENT OF ADULT NORMAL		WEIGHT OF INFANT (GRAMS)	BLOOD LOSS THIRD STAGE LABOR C.C.	ADMISSION CELL VOL.
	MOTHER	INFANT			
1	100	22	3650	140	35
2	100	25	3770	90	37
3	90	35	4100	50	37
4	70	25	3090	20	32
5	80	15	3550	180	38
6	70	25	3540	70	46
7	60	30	3930	290	30
8	100	35	3880	195	33
9	50	10	3570	300	37
10	70	30	3560	270	38
11	25	10	3300	45	36
12	60	20	3680	250	33
13	55	25	3860	120	37
14	100	25	3090	100	35
15	70	15	3940	75	35
16	70	25	3450	500	33
17	85	45	4060	160	36
18	75	15	3330	75	40
19	100	25	3700	300	38
20	100	22	3300	450	36
Average	77.8	23.5	3617	165	36

Table I shows the average prothrombin level in the mothers as 77.8 per cent (range 25 to 100 per cent of the adult normal), and the average volume of packed cells as 36 per cent; the latter value is considered a normal figure for pregnant women at term. It will be recalled that the average is about 42 per cent in non-pregnant patients, so that the lower value in pregnancy is probably due to an associated hydremia. The mothers had an average blood loss of 165 c.c. (range 20 to 500 c.c.). The patient in Case 11 had a prothrombin concentration of 25 per cent of the normal, just on the hemorrhage border line for patients with jaundice, and had a blood loss of only 45 c.c., during the third stage of labor.

As shown in Table I, the average prothrombin concentration in the infants was 23.5 per cent, with a range from 10 to 45 per cent, which is one-third to one-fourth as much as the amount present in the mothers. The infants were all full term, with an average weight of 3617 Gm. No infant developed hemorrhagic disease. This is of further significance in Cases 5, 9, 11, 15, 18, with unusually low prothrombin values of between 10 and 15 per cent of the adult normal.

The volume of packed cells, hemoglobin, red cell count, and icteric index are shown for 14 of the infants in Table II. The red cell count averaged 5,500,000 per c.mm., and the average hemoglobin was 126 per cent, using the Hellige hemometer (14.5 Gm. = 100 per cent). These findings are within the normal range for the newborn, but considerably higher than are found in the adult. The volume of packed cells was 54 per cent, which is higher than the adult average of 42 per cent. The icteric index was also elevated to an average of 15 units, which is not unusual for a normal newborn infant. The low concentration of prothrombin in the infants is not due to plasma dilution. Is it due to failure of formation?

Cases 1, 4, 6, 7, 8, 16, 18, with an average icteric index of 17 units (excluding No. 16, and 18 on whom no determination was made) had clinical evidence of jaundice.

TABLE II. ADDITIONAL BLOOD STUDIES (CORD BLOOD) ON 20 NEWBORN INFANTS

CASE	RED CELL COUNT	HEMOGLOBIN (PER CENT)	CELL VOLUME (PER CENT)	ICTERIC INDEX (UNITS)
1	5,000,000	114	49	30
2	4,940,000	126	50	15
3	4,900,000	130	54	15
4	5,900,000	126	55	15
5	5,900,000	120	59	Hemolyzed
6	5,920,000	120	53	15
7	5,300,000	124	52	10
8	5,500,000	120	44	15
9	5,600,000	134	58	10
10	7,000,000	132	58	10
11	5,000,000	124	50	10
12	4,600,000	124	52	15
13	5,140,000	120	52	15
14	6,300,000	142	60	15
15			57	20
16				
17				
18	Not studied			
19				
20				
Average	5,500,000	126	54	15

DISCUSSION

Our determinations confirm the report of Brinkhous, Smith, and Warner in 1937, and have already been referred to in the literature by Hellman and Shettles, as a personal communication. Although a series of 20 cases is small, the consistency of the low prothrombin concentration of the infant as compared with that of the mother is rather striking. The infant has from one-third to one-fourth as much prothrombin as have the normal adult controls. The difference in the prothrombin of the blood plasma of the mothers and infants indicates that the molecule of prothrombin does not pass through the placental membrane. This suggests that the fetus produces its own prothrombin.

The comparison of prothrombin levels of the infant with adult values may be improper, and is not done with regard to other blood determinations on infants, such as hemoglobin, red count, and volume of packed cells; but normal values for the newborn have been established. Should not the low prothrombin concentration found in the newborn as indicated by the average value of only 23.6 per cent obtained in this study, or 26 per cent obtained by Brinkhous, Smith, and Warner be accepted as the normal for the newborn?

The low prothrombin values found in the infants may be due to the liver on the basis of hepatic insufficiency, which has been offered by Waugh and his co-workers as the explanation for the development of hyperbilirubinemia and icterus neonatorum. In this respect the fetal circulation is perhaps of great significance since the ductus venosus permits blood to by-pass the liver by emptying into the inferior vena cava. After the umbilical cord is ligated, several days must elapse in order for the portal circulation and liver to assume the production of pro-

thrombin and the excretion of excessive bilirubin. In the meantime, hyperbilirubinemia occurs with and without clinical icterus, and a further lowering of the "physiologic hypoprothrombinemia" takes place in the first days of life as shown by Warner and co-workers, and by Owen and his associates.

CONCLUSIONS

1. The prothrombin concentration of 20 parturient women at term, and of the cord blood of their infants was determined by the method of Warner, Brinkhous, and Smith. The concentration expressed in per cent of the adult normal was 77 for the mothers, and 23 for the infants. This difference suggests that the prothrombin molecule does not cross the placental membrane.

2. Readings as low as 10 to 15 per cent of the adult normal were observed in several infants without evidence of hemorrhagic disease. The critical levels in the newborn must be determined by further study.

3. One mother had a low value distinctly in the bleeding range for jaundiced patients, with a minimal blood loss in the third stage of labor.

4. The low levels in the infant are evidently not due to dilution, since the volume of packed cells was not reduced, and may instead be the result of failure of production on the basis of liver insufficiency. The further reduction occurring in the first days of life is probably on the same basis.

5. In making statistical comparison of prothrombin concentration as determined by various investigators, attention must be given to the source of blood (cord or jugular), the day of life, and the method used for the determinations. This will do much to clarify the present conflicting situation as to whether the low prothrombin levels at birth are normal.

6. Consideration must be given to the quality as well as the quantity of prothrombin. The speed of convertibility may explain why less than one infant in one hundred develops hemorrhagic disease. The low prothrombin level in the cord blood at birth may predict such a tendency.

7. Hypoprothrombinemia and hyperbilirubinemia of the newborn are probably caused by hepatic insufficiency. The importance of the patent ductus venosus in this connection was emphasized.

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OPERATION FOR UTERINE RETRODISPLACEMENT AND PROLAPSE BY REDUCTION AND ATTACHMENT OF THE ROUND LIGAMENTS

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ONE must advance an adequate reason, if not an excuse, for introducing another operation for retrodisplacement of the uterus. In the present instance, dissatisfaction with the admittedly infrequent shortcomings of the standard operations prompted the development of a modified technique which possesses definite advantages. I do not share with Dannreuther[1] his partiality for the Baldy-Webster and Gilliam-type operations, but agree rather with Graves'[2] statement that no operation which depends upon shortening of the round and uterosacral ligaments can be depended upon to withstand gestation and parturition. In addition, the Baldy-Webster maneuver predisposes to the formation of adhesions in the cul-de-sac which may readily defeat the operation's purpose; furthermore, the reported incidence of herniation through the broad ligament openings is now so convincing that the technique should be employed only with the greatest care and proper misgiving. Similarly, the Gilliam operation has the following defects: The creation of three pockets between the round ligament emplacements and at the sides which favor herniation and ileus; in the presence of inflammatory disease, a fixed barrier or shelf vertically dividing the pelvis, may result from adherence of the round and broad ligaments and the fundus to the abdominal wall; in addition, many patients complain of pain in the region of the internal ring which persists for several months after the Gilliam type operation. We, therefore, prefer the principles set forth by Olshausen, and advanced by Graves. In the Olshausen operation, the thickest, most dependable part of the round ligaments, close to the corpus, is fixed to the anterior abdominal wall by a permanent suture through the peritoneum, muscle, and fascia. This operation is, in effect, a ventral fixation of the uterus, since the segment of round ligament employed must be considered a projection of the corpus. Because, as Dannreuther has indicated, many suspensions became fixations, we prefer to discard both terms in favor of the more inclusive name, attachment.

OLSHAUSEN OPERATION

The disadvantages of this procedure may be enumerated as follows: Two-point fixation, with the resulting three interspaces which invite intestinal incarceration; restricted mobility of the uterus and reduction of bladder space, as mentioned by Dannreuther and others, which is common to all operations for retrodisplacement or prolapse; reduction of bladder space which cannot occur if the attachment is sufficiently high

on the parietes—a point emphasized in the operation to be described. A fourth objection to this admirable operation is its failure to reduce or shorten the round ligaments.

REDUCTION-ATTACHMENT OPERATION

Our objective has been a method which permits reduction or shortening of the round ligaments, utilizes the strong proximal portions of the round ligaments, and allows attachment of the uterus at a single point to the abdominal wall. This we have evolved by attachment of the corpus through the direct medium of the round ligaments. Secondary objectives were facility of operation and use of a single suture for the completed procedure.

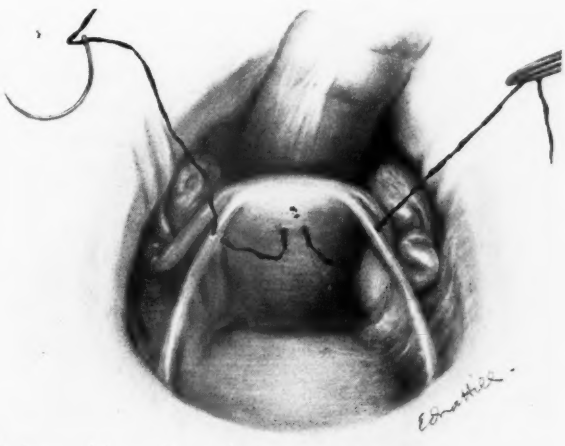

Fig. 1.—Suture of four strands of No. 24 cotton thread passed through round ligaments 1.5 cm. from corpus and through a segment of corpus.

OPERATIVE TECHNIQUE

A 14-inch suture composed of four strands of No. 24 plain black spool cotton thread (3) (or an equivalently strong single silk or linen suture) is passed through a round ligament 2 cm. from the corpus, through a 1 cm. segment of the uterus 2 cm. below its fundus, and through the other round ligament at the same level. The suture ends, of equal length, are tied in a single square knot which brings the ligaments together at a point of attachment. The needle is then introduced through the round ligaments at the midpoint from corpus to internal rings, and the suture again tied to the original end. Thus the ligaments are reduced by half. Clamps are placed on the peritoneal edges 6 cm. above the lower wound angle. The needle is passed from within-out through peritoneum, muscle, and fascia on the left side of the incision, and returned to the abdomen from without-in through fascia, muscle, and peritoneum of the right side. The suture is then tied to the original long end within the peritoneal cavity, thus completing the attachment. It is seen that the directional stress or support is through the strongest units of the round ligaments to the corpus itself. The 4-strand cotton suture can be depended upon for permanency. Adherent attachment will also occur.

In prolapse, the usual plastic vaginal repairs are done first. We have not found it necessary to plicate or sew together the uterosacral ligaments. In severe prolapse, the attachment is made as high as the fundus can be extended, without tension. Removal of all or part of the corpus will frequently make

possible a still higher relative attachment in third and fourth degree prolapse with relaxed abdominal musculature.

It is indicated that this operation does not aim at anteflexion. The attachment is on the anterior surface of the uterus, so that growth during gestation will not be hampered. Since the attachment-suture closes and frequently inverts

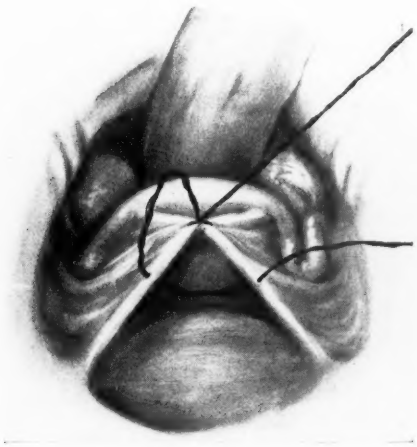

Fig. 2.

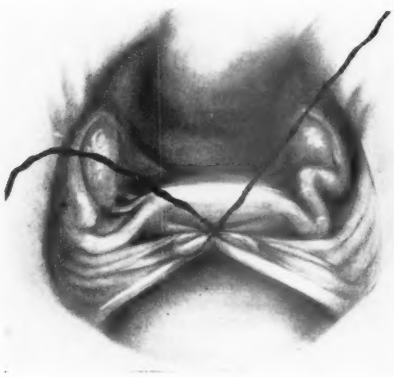

Fig. 3.

Fig. 2.—Suture tied and passed again through round ligaments at midpoint to internal ring.

Fig. 3.—Second tie. Point of uterine suspension is 2.5 cm. below top of fundus.

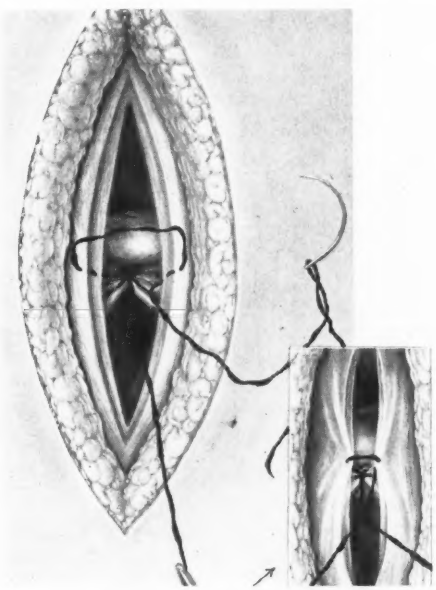

Fig. 4.—Same suture passed through peritoneum and fascia on both sides of incision 6 to 8 cm. above lower angle of wound. *Inset:* Suture tied to original long end within the abdomen.

the peritoneum at the point of fixation, unusual care must be exercised in sewing the peritoneal edges to prevent the formation of a cleft or defect which would predispose to ventral hernia. Presence of the bulk of folded round ligaments at the attachment point emphasizes the need for meticulous closure.

RESULTS OF OPERATION

This technique has been developed over a four-year period in 120 patients. In its present form it has been used for two years, the quadruple cotton suture for one year. Our opportunity for re-examination is necessarily limited. No failures have been detected. The few patients (6) subsequently seen in parturition and puerperium have not had dystocia due to operation and have not had recurrence of retrodisplacement. No sinuses have resulted. The postoperative and convalescent courses in cases not complicated by other pelvic pathology have been relatively comfortable.

RÉSUMÉ

1. A simple, rapid technique is presented for reduction of round ligaments and single-point attachment of the uterus. Pocket formation of the Gilliam and Olshausen operations is avoided.

2. This operation has the merits of the Olshausen procedure and apparently none of its disadvantages.

3. A single 4-strand cotton suture is utilized.

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THE NAUSEA AND VOMITING OF PREGNANCY DUE TO ALLERGIC REACTION

A Study of 192 Cases

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THIS report is a summary of work done subsequent to a publication in 1938,[1] theorizing that the nausea and the vomiting accompanying pregnancy are due to an allergic reaction of the patient to the secretion of her own corpus luteum graviditatis. A report of 192 cases is presented to substantiate this theory further.

From one-half to two-thirds of all obstetric patients experience nausea and vomiting in some degree during the first trimester. The symptoms may vary in severity from the mild case, so frequently seen, in which there is morning sickness, with or without vomiting, to the moderate case, in which there are nausea all day long, frequent vomiting, and extreme discomfort for weeks. A few cases will advance to a true hyperemesis gravidarum with a definitely serious prognosis.

I believe the patient presenting nausea and vomiting of pregnancy has inherited an allergic tendency and has become sensitive to her own corpus luteum secretion during her menstrual life or from the corpus luteum of a previous pregnancy. I believe the symptoms of nausea and vomiting develop as an allergic reaction to the secretion of the corpus luteum of pregnancy and disappear after the gland ceases to feed its secretion into the patient's body in such abundance. The results of this research strongly indicate the presence of a luteal secretion other than progesterone which is responsible for this allergic manifestation.

The corpus luteum, with impregnation, continues to develop instead of taking on the customary retrogressive changes during and after menstruation. The corpus luteum of pregnancy develops to a size much larger than the false corpus luteum; the colloid is more abundant in the organ, and the granulosa cells are larger than before pregnancy.[2]

Considering that the development of the nausea and vomiting and the development of the corpus luteum of pregnancy occur at the same time and that the time of disappearance of symptoms coincides with the time of retrogressive changes in the gland, patients with nausea and vomiting of pregnancy were given intradermally injections of various corpus luteum extractions. Intradermal reactions developed in direct proportion to the degree of nausea and vomiting present. Likewise, patients treated with desensitizing doses of these extractions were relieved of their symptoms.

To avoid confusion in the following case reports, the term "progestin" will be used to indicate the natural hormone of the corpus luteum as it occurs in partially purified extracts. The term "progesterone" will be used for the synthetically produced pure hormone ($C_{21}H_{30}O_2$) dissolved in oil.

TECHNIQUE OF INTRADERMAL TESTS

The technique of intradermal testing for sensitivity was to cleanse the skin with alcohol and to inject intradermally from 0.02 to 0.03 c.c. of the test solution. Twenty to thirty minutes later reactions were recorded, calibrating them from negative to plus four, according to the size of the wheal and the surrounding erythema produced, just as in intradermal injections of any food, drug, pollen extract, or animal dander to determine a patient's degree of sensitivity. The majority of tests were made on the volar surface of the forearm. Numerous products were used in the skin tests, but the most satisfactory was found to be progestin in sterile cottonseed oil, as this oil is less irritating when injected intradermally than is oil of sesame, almond oil and peanut oil used in some commercial products. A control test was made in each case by injecting intradermally a like amount of the sterile oil used, to rule out cases of sensitivity to the oil alone. Many of the cases were rechecked, using a glycerin extraction of the corpus luteum, but this was given up as impractical as the solution was unstable and the glycerin was very irritating to some skins.

Since it is known that the placenta also secretes progesterone and that the daily output of urinary pregnanediol rises abruptly during the second and third trimesters, we must assume that these patients presenting nausea and vomiting are sensitive to some other luteal secretion than progesterone, else they would become more and more nauseated as their

pregnancy advances. Because of this fact, patients were intradermally tested with synthetic progesterone in oil and with progestin in oil. Intradermal reactions to the natural progestin were in almost every case directly proportional to the degree of nausea and vomiting the patient presented. Reactions to the intradermal synthetic progesterone were negative in most cases and followed no proportional ratio to the degree of the symptoms.

Commercial products of progestin are prepared by alcoholic extraction of corpora lutea and purification of the oil. The estrins are removed by subsequent chemical treatment. This product is assayed for its progesterone content alone but must contain some other hormone to explain the results obtained in this research. I do not believe that the allergen is the gonadotropic hormone of pituitary origin or of chorionic origin, else we would have, with the former, hyperemesis with many cases of natural and surgical or radiation menopause and with the latter would have hyperemesis with chorionepithelioma, for in these conditions the gonadotropic hormone level increases tremendously, even above that of the nausea and vomiting of pregnancy.

Injections of large doses of natural progestin into rabbits failed to give a positive Friedman test.

As a further control of the intradermal tests, 20 patients with skin sensitivity to progestin were also tested with intradermal estrogen and with the gonadotropic fraction from pregnant urine. Skin reactions to these products were essentially negative and in no ratio to the degree of nausea and vomiting present.

CASE REPORTS

Series A.—A series of 42 pregnant patients with nausea and vomiting, and in the first trimester, was tested for skin sensitivity to progestin. Ages varied from eighteen to thirty-nine years. Parity range was from primipara to nonigravida. Menstrual histories were essentially normal. A very high percentage of patients had been severely nauseated with previous pregnancies. Their skin reactions to progestin varied in direct proportion to their degree of nausea and vomiting, from one-plus to four-plus. Sixteen per cent gave a history of personal allergy (hives, hay fever, asthma, migraine, or urticaria), and 25 per cent of them gave a history of allergy in the family.

Twenty-two of these patients were observed to the termination of the pregnancy. Twenty had normal children at term, 13 being male and 7 female. Two had premature births, one at four and one at six months' gestation. One had a threatened abortion at six months. There were no cases of toxemia of late pregnancy.

Series B.—There were five nonpregnant multiparas with a history of moderate to severe nausea and vomiting with previous pregnancies, and with no history of family allergy. Two had a history of personal allergy, who gave two-plus and three-plus skin reactions to progestin.

Series C.—Four virgins, with no history of family allergy, one with premenstrual migraine, and two with premenstrual nausea, gave two- and three-plus skin reactions to progestin intradermally.

Series D.—Twenty-three pregnant patients in the first trimester, who had no nausea or vomiting with the present or any previous pregnancy, were tested intradermally as outlined above. Ages varied from 18 to 38 years and the parity range

was from primipara to quintipara; 4.3 per cent gave a history of family allergy. None had a history of personal allergy. One patient had a one-plus skin reaction and 22 were negative.

Series E.—Five nonpregnant multiparas with a history of having had no nausea or vomiting with previous pregnancies, no history of menstrual abnormality, and no history of allergy, either personal or familial, had negative skin reactions to progestin intradermally.

Series F.—Six virgins with no history of menstrual abnormality or allergy had negative skin reactions to progestin.

Series G.—If the theory upon which this research is based is true, girls before puberty, theoretically, should react negatively to intradermal corpus luteum extracts, never having had any luteal function. Fifty-six girls, chosen at random from pediatric wards, none seriously ill, were tested in the manner described. Ages ranged from two months to thirteen years. All but three patients were less than 10 years of age. Seven children had one-plus reactions and 49 were entirely negative in reaction.

Series H.—Fifty-one cases of moderate to severe nausea and vomiting of pregnancy were tested intradermally with progestin for sensitivity and treated along the lines of allergic desensitization to the corpus luteum hormone using graduated doses of progestin in oil intramuscularly. Fifty of the cases were white women, one a negress. All were in the first trimester of pregnancy. Cases were divided equally among charity patients and private patients of fair to excellent financial and social status. About half of the pregnancies were desired and half unwanted. Patients varied in age from 17 to 42 years and in parity from primipara to octipara. All had essentially normal menstrual histories except a few cases of premenstrual migraine, premenstrual nausea, and dysmenorrhea.

Fourteen cases were classified in severity as four-plus (nauseated all of the time and vomiting all ingested food and fluid). Twenty-one were classified as three-plus (nauseated all day and vomiting three or four times daily). Sixteen were classified as two-plus (nauseated all day and vomiting none to two times).

TREATMENT

Patients were treated with some variation but the average was to begin with one half international unit of progestin in oil. One day later one unit was given. Treatment then followed at forty-eight- to seventy-two-hour intervals until the patient stopped vomiting, increasing the dose gradually to three or four units if necessary. When the vomiting ceased, the dose was not further increased and the interval between doses gradually lengthened to five days. As soon as nausea had disappeared, the dose was somewhat reduced and continued at five- to seven-day intervals for two or three doses. Some patients responded so promptly that the dose was not increased beyond one and one-half units. The patient's response to treatment directed the rapidity and degree of increase and decrease of dosage. A few patients were found who were apparently very sensitive to the drug and could not tolerate large doses. In these cases, too great an increase would markedly increase the symptoms for a few hours. Generally speaking, the patients with four-plus skin reactions required larger doses and a greater number of total doses for relief than those with lesser skin reactions.

The average total amount of the drug used was 9.05 international units per patient, given in an average of 7.3 total doses. Results were excellent in 44 (87.4 per cent) of the cases, fair in 2 cases (3.9 per cent), and poor in 5 cases (9.8 per cent). The average length of time from beginning treatment until all vomiting ceased was 4.8 days. The longest time was nine days. The average length of time from beginning treatment until relief from nausea was 8.05 days. The longest time was nineteen days.

Twenty-six per cent of the patients in this series gave a history of personal allergy other than the nausea and vomiting. Thirty-six per cent gave a history of allergy in the family. Forty patients were observed throughout their pregnancy. Of these, 4 had premature births, 3 at three months' gestation and one

had a Voorhees bag induction at seven months' gestation because of a severe eclampsia. Eighteen babies were females and 22 were males. There were no maternal deaths and no fetal deaths except these 4.

Of these 51 patients, 10 were given synthetic progesterone at the beginning of treatment. Nine showed no improvement and one had very slight improvement after one week. Treatment was then changed to natural progestin without telling the patient of the change. There was marked improvement in a few days in each patient. Another 10 patients were started on treatment with sterile oil injections. One of these patients showed a very slight improvement and 9 no improvement after one week. Again, without telling the patient, the treatment was changed to progestin with marked improvement in a few days.

Eight patients had had phenobarbital, one had had intravenous calcium gluconate and another had had six doses of an unknown drug hypodermically before treatment as described above was begun. None had had relief from their symptoms. The remaining 43 patients had had no treatment. No treatment other than that described was used in any of these cases. Forty of the series were treated as ambulatory patients. Eleven were kept in the hospital in order that they might receive their treatments and be observed accurately. Patients were kept in undarkened rooms, were allowed visitors and radios, and were sent general diet trays. Ambulatory patients were instructed to do and eat as they desired.

Four of this series were given intradermal tests before pregnancy occurred. Positive reactions were obtained in direct proportion to the degree of nausea and vomiting that developed when pregnancy ensued, although the patients were not told what the tests indicated.

Nineteen patients had four-plus skin reactions, 17 had three-plus reactions, 13 two-plus reactions, 1 a one-plus reaction, and 1 a negative reaction. The patient with the negative reaction was definitely psychic and the one-plus reaction was in a patient with a pituitary syndrome (basophilic adenoma), who although the skin reaction was slight, was greatly benefited by the treatment. With few exceptions the skin reactions were directly proportional to the severity of the symptoms in each case.

Twenty patients from Series "A" were treated with synthetic progesterone in doses similar to that used in Series "H." Four of these patients were slightly improved and 16 had no improvement whatsoever.

Of the 5 patients in Series "H" who had no improvement from the treatment, one was a known neurotic who had had severe vomiting with three previous pregnancies. Her skin reaction was negative and treatment gave no relief. Psychic treatment effected a rather spectacular cure. Two of the case reports were pregnancies in the same patient on successive years. Her skin test was three-plus. She had intense nausea but was seldom able to vomit. Treatment did not effect any improvement. Psychotherapy failed to be of any value after the other treatment was discontinued. Symptoms subsided in the fourth month of pregnancy.

The fourth patient had a positive skin test but was very neurotic and informed us she could tell the exact date on which she would cease vomiting. She missed her calculations two days. The remaining patient came to the hospital in a state of starvation, acidosis, and avitaminosis, having vomited for five weeks with almost continuous vomiting for four days. This patient had to have fluids, glucose, vitamin concentrates, and sedatives to control her vomiting. She was also given progestin and had no reoccurrence of her trouble. She would have had no reoccurrence anyway in all probability as she was then entering her fourth month of pregnancy.

Of the 2 patients with only fair results, one, an earlier case in the series, had inadequate dosage. The other did not respond well although treatment was adequate. Both patients had four-plus skin reactions. Vomiting was controlled in each case but the nausea continued until the fourth month of pregnancy.

An interesting notation was that about 40 per cent of the patients in Series "A," the untreated series, complained as late as five or six weeks after the intradermal injection that when they became nauseated severely the area of

intradermal injection again became irritated and formed a wheal with a surrounding erythema and intense itching. This reoccurrence of the positive skin test occurred in all 4 of the patients in Series "C," five or six days following ovulation. I know of no way to explain this other than that the solution injected, being an oily one, is absorbed very slowly and part of it remains in the skin for a protracted time, causing a reoccurring positive test when the corpus luteum secretion of the patient is more abundant.

COMMENT

From these results I believe this method of diagnosis from intradermal testing will prove of value in eliminating the small percentage of psychic cases of vomiting from those definitely ill. By skin tests one may prognosticate which patients will suffer from nausea and vomiting early in pregnancy, or perhaps, even before pregnancy occurs and may use this method of treatment as a preventive measure. I believe this method of treatment, if begun early in the nausea and vomiting, will prevent practically all of the severe cases of hyperemesis too frequently seen, in addition to relieving countless thousands of women each year from a most uncomfortable period of weeks of nausea with or without vomiting.

Although desensitization to progestin can prevent hyperemesis and can cure the earlier cases, I doubt if it will be sufficient in itself to cure the patient who is not seen until late in pregnancy, for here we are dealing with a patient who has missed her early treatment and is now sick from starvation, acidosis, avitaminosis, and severe dehydration. No doubt, it will be necessary to replace fluids and vitamins and give sedatives to these patients; however, if still in the first trimester, desensitization to her corpus luteum may be a useful adjunctive treatment. Most of these late cases are entering the second trimester and as soon as this starvation and dehydration is remedied, the patients will be free from nausea and vomiting, as the corpus luteum has then begun to retrogress and its secretion has lessened or disappeared—an analogous condition to the hay fever sufferer following the first heavy frost. This fact alone is perhaps the answer to why patients who have vomited for weeks finally are taken to the hospital and recover spectacularly with replacement of fluids, glucose, and with sedatives. They were sick, by the time of hospital admission, not from an allergic nausea and vomiting of pregnancy but from a secondary condition of starvation produced by the nausea and vomiting.

This treatment is economical, the cost of the drug necessary for treating the average case being less than ten dollars and the duration of the treatment comparatively short. It is without danger of ill effects.

The results, both diagnostic and therapeutic, from natural progestin versus the lack of results using synthetic progesterone would indicate strongly the existence of another hormone of the corpus luteum, other than progesterone, in the products made from luteal extractions, now commercially available. It will be interesting to see what will be learned by further analysis of these luteal extractions.

In summarizing the literature, there is further evidence that the nausea and vomiting of pregnancy is allergic. Hirst[3] was the first to associate the nausea and vomiting of pregnancy with the function of the corpus luteum. Duplication of his work has not produced uniform results, however, because the gland extracts available until recently were unstandardized and of inadequate potency. It can be assumed that he was able to relieve his patients, not by giving them a secretion in which they were deficient, as he theorized, but by desensitizing them to some degree and relieving them of their allergic reaction.

Saxon and Stoll[4] report 75 patients treated with autohemotherapy, theorizing that the small amount of blood injected into the tissues is in the nature of a desensitizing process to a certain toxin which is elaborated and absorbed into the blood stream of the pregnant woman. In their series, the serum of the pregnant patient probably contained sufficient luteal hormone to effect a desensitization when injected.

Freeman, Melick and McClusky,[5] and Kotz and Kaufman[6] report good results with the administration of adrenal cortex, both orally and hypodermically. It is not unlikely that results from administration of this substance are brought about by treatment of the allergy of the patient alone, as Pottenger and Pottenger[7] report 50 children with asthma treated successfully for one year by the use of adrenal cortex.

Hawkinson[8, 9] reported 150 patients treated with estrogen with good results. He gave severely ill patients daily injections of 10,000 units of theelin in oil. Numerous observers have proved the depressing activity of the estrogens on anterior pituitary function, which no doubt explains the results with this therapy, i.e., depressing the luteinizing factor of the pituitary should decrease the secretion of the offending hormone of the corpus luteum. As further proof of this explanation, Brindeau, Hinglais and Hinglais[10] report 15 patients with nausea and vomiting of early pregnancy in which the titer of the gonadotropic hormone (prolan B) of the blood was above normal in direct proportion to the degree of the symptoms. With cure of the nausea and vomiting, all titers returned to normal.

In hyperemesis gravidarum, Siebke[11] was unable to detect any abnormality in concentration of the estrogenic substance of the blood. Thus, it seems that this treatment as recommended by Hawkinson, using estrogen, is not without danger of inducing abortion. Costa and Cantilo[12] report that abortion frequently followed administration of large amounts of theelin when corpus luteum was not subsequently used.

SUMMARY

1. The nausea and vomiting of pregnancy develop at the same time at which the corpus luteum of pregnancy reaches an appreciable size. The symptoms disappear at about the time the gland is known to begin retrogressive changes.

2. In 98 patients with nausea and vomiting of pregnancy in varying degrees, a cutaneous reaction directly proportional to the degree of the severity of the symptoms developed when injected intradermally with from 0.02 to 0.03 c.c. of progestin (natural) in oil.

3. A control series of patients who were not nauseated and in the pregnant state gave negative cutaneous reactions when tested in a like manner.

4. A series of young girls, before puberty, likewise gave negative reactions to intradermal progestin.

5. 91.2 per cent of 51 patients treated with progestin in oil along the lines of allergic desensitization were relieved of their symptoms.

6. A control series of patients treated and skin tested with synthetic progesterone in oil failed to react or to be relieved of their symptoms.

7. A high percentage of the patients with nausea and vomiting of pregnancy either had other diseases of allergy or gave a family history of allergy.

CONCLUSIONS

1. The nausea and vomiting accompanying pregnancy are due to an allergic reaction of the patient to the secretion of her own corpus luteum of pregnancy.

2. The luteal hormone acting as an allergen is not progesterone but is an unidentified hormone of the corpus luteum.

3. Desensitization may be accomplished by injection of graduated doses of progestin in oil, thus alleviating or stopping the patient's symptoms.

4. Intradermal testing may determine, even before pregnancy, whether a patient will or will not be nauseated when pregnant by determining whether or not she is sensitive to her own secretion.

I wish to express my extreme gratitude for the generous quantities of "proluton," supplied by the Schering Corporation, "lipolutin," supplied by Parke, Davis & Co., "progestin in oil," supplied by Eli Lilly & Co., "progestin in oil," supplied by The Upjohn Co., "progestone," supplied by G. W. Carnrick Co., and for a quantity of especially prepared progestin in glycerin furnished by The Upjohn Co. Also for specially prepared ampoules of sesame oil, peanut oil, cottonseed oil, and almond oil supplied by these same firms for use in control injections.

I wish to express my appreciation for the great amount of cooperation and assistance given by members of the Obstetrics Staff and the Interne Staff of the University of Oklahoma School of Medicine and University Hospitals.

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Oklahoman Building

Olivella, J. R., and Feo, J. A. R.: Acute Torsion of the Gravid Uterus, Rev. Cubana de obstet. e ginec. **1:** 96, 1939.

A 27-year-old woman in the eighth month of her third pregnancy presented the isolated symptom of an intense continuous pain, generalized throughout her abdomen. Palpation and auscultation of the abdomen were difficult, due to spasm of the musculature. A peaklike elevation was noted in the epigastric region. At operation a 90° rotation of a "cordiform" uterus was found. The organ was intensely cyanotic and a greatly distended left cornu apparently caused the elevation noted on inspection of the abdomen. A live fetus was removed through an incision over the anterior aspect of the left cornu.

Hysterectomy is indicated when the viability of the uterus seems endangered, but was not necessary in this case.

R. J. Weissman

THE EFFECTS OF STILBESTROL UPON LACTATION*

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THE physiologic processes involved in lactation are essentially endocrine in nature. The development of the lobule-alveolar system proceeds under the influence of the ovarian hormones.[1] The initiation of lactation depends upon the anterior lobe of the pituitary, for hypophysectomy during late pregnancy will prevent milk secretion post partum.[2] The anterior hypophysis also is essential for the maintenance of established lactation, for the removal of the anterior lobe during this time will result in a rapid cessation of milk secretion.[2] While the initiation of lactation appears to be under purely hormonal influence, the maintenance of established lactation requires a neurogenic factor in addition to the hormonal one. This is the reflex stimulation of the anterior pituitary by the act of suckling for the further secretion of milk. Clearly, then, the process of lactation resolves itself into two fundamental mechanisms: first, the initiation of lactation by hormonal factors, and second, the maintenance of established lactation by both hormonal and neurogenic agencies. The evidence is both experimental and clinical.[3]

The initiation of lactation post partum has been explained by Nelson in the following manner:[1] The presence of unusually large amounts of estrogen during the latter part of pregnancy inhibits the secretion and action of the lactogenic principle (s) of pituitary. With parturition, the level of the circulating ovarian hormones drops precipitously; the inhibiting influences are thus removed, lactogenic hormone is secreted, and lactation occurs. As experimental proof of this, Nelson offered the following data: Injections of large doses of estrogen into the guinea pig soon after parturition would hold milk secretion in abeyance during the injection period. Lactation, however, would occur within two days after cessation of treatment, or if lactogenic hormone were administered simultaneously with the estrogen. On the other hand, the dosage of estrogen could be so increased that even large doses of the lactogenic hormone would be ineffectual.

Inhibition of lactation by large doses of various estrogens in the experimental animal has been claimed by several workers. Their evidence has been cited as confirming the estrogen inhibition theory. Critical analysis of the results brings to light several serious objections and discrepancies. In the first place, most of the reports dealing with the rat and the mouse showed that a good many of the litters were reared but were stunted in growth. Young rats and mice are particularly sensitive to estrogens, which adversely affect body growth,[4] upon which, in turn,

*Presented, in part, by Dr. A. R. Abarbanel at the Section on Obstetrics and Gynecology, New York Academy of Medicine, February 27, 1940.

body weight depends. Since estrogens are readily secreted in the milk,[5] the evidence in these animals may not be accepted as conclusive proof of inhibition of lactation. Second, estrogens are known to affect the composition of the milk, increasing the amount of fat and nonfatty solids.[6] Whether these very immature animals are capable of digesting an altered milk is problematical. Moreover, the mothers were found to have lost considerable weight, indicating an additional systemic response in the maternal organism that was detrimental to her well being.[7] On the other hand, large amounts of estrogen injected over a period of six days were found to be without effect upon the amount or duration of secretion in the lactating rabbit.[8] Others have reported a reduction, but not suppression, of lactation with large doses of estrogen in the rat,[7, 9, 10] goat,[11] and cow.[6, 12]

The hypothesis advanced by Nelson also fails to explain the well-known fact that lactation may continue through successive pregnancies in several species including the rat, rabbit, goat, and the human being. In man especially, increasingly larger amounts of estrogen are produced during pregnancy. In the cow and the rabbit, lactation occurs some twenty and six days, respectively, before parturition.

All in all, the experimental evidence for the inhibition and suppression of lactation by estrogens is far from decisive. The evidence has recently been critically reviewed by Turner.[3]

In spite of the rather inconclusive experimental data, many clinical reports have appeared, claiming hormonal inhibition and suppression of lactation in the human being. The estrogens (estradiol benzoate, estrone, and lately stilbestrol) have been used in varying dosage.

Sawizki,[13] using 200 to 800 I.U. of estrone plus 100 R.U. of chorionic gonadotropin, reported successful inhibition of lactation in the human being. Others, finding this dosage far too small, have recommended 30,000 to 50,000 I.B.U. (international benzoate units) of estradiol benzoate as a daily or total dosage over a period of one to five days.[14-17] In a detailed study of the question of dosage, Mayor[18] found that not only was 1,000 I.U. of estrone (0.1 mg.) insufficient, but even 10,000 I.B.U. of estradiol benzoate (1 mg.) administered daily for six to eight days was not enough. Using 250,000 I.B.U. of estradiol benzoate (25 mg.) in oil as a single injection on the first day post partum, he found that of 14 patients so treated, 4 (29 per cent) had no filling, 8 (57 per cent) filled without pain between the fifth and seventh days, while 2 (14 per cent) became fully engorged on the eighth and twelfth days post partum, respectively. Lehman,[19] using a single injection of 100,000 to 150,000 I.B.U. of estradiol benzoate (10 to 15 mg.) the first day postpartum, reported that in a series of 75 cases, 32 per cent had no engorgement, 59 per cent had some secretion or painless filling, while 9 per cent became engorged. For the suppression of established lactation, he found that a single dose of 20 mg. of estradiol benzoate (200,000 I.B.U.) was necessary to yield results in 88 per cent of his series.

The dosage recommended for stilbestrol, the orally active and highly potent synthetic estrogen,* has also been quite variable, ranging from 6 to 80 mg.[20-22]

Careful analysis of the clinical reports reveals certain inadequacies as a result of which the claims for hormonal inhibition and suppression

*One milligram of stilbestrol is approximately equivalent to 2.5 mg. of estrone or 25,000 I.U. One milligram of estradiol benzoate equals 10,000 I.B.U.

of lactation in the human being may not be properly evaluated. In the first place, the baby was removed from the breast simultaneously with the administration of the hormone. It is a well-known fact, however, backed up by abundant experimental and clinical evidence, that the maintenance of lactation is dependent upon the nervous stimulus of suckling, or its equivalent.

Furthermore, practically no differentiation seems to have been made between the onset of lactation and painful engorgement of the breasts. These are two distinct phenomena that are not synonymous at all. Painful engorgement is caused by lymphatic and vascular stasis, not by distention of the ducts by milk.[23]

Because of the inconclusive experimental and clinical data, the following studies were carried out in order to clarify the effects of estrogens upon lactation in the human being. The estrogen chosen was stilbestrol since it retains most of its potency on oral administration while the latter route requires a minimum of nursing care.

PROCEDURES AND RESULTS

Three hundred and fifteen parturient women were studied. These were divided into several groups. A control group was chosen of 50 apparently healthy mothers who had had normal spontaneous deliveries of normal active babies. Each gave a history of having adequately nursed their previous babies for at least three months. The daily amount of mother's milk was computed from weighing the baby before and after each feeding. The babies were allowed to nurse for twenty minutes five times a day, at four-hour intervals. As the babies did not go to breast at 2 A.M., each received a dilute formula of three ounces at this time.

In this manner, the average normal amount of breast milk obtained by the baby in five daily feedings was found to total from 8 to 14 ounces daily. A daily individual variation was found in practically every patient, ranging from one to as much as six ounces. Interesting, too, is the almost universal drop in the amount of milk obtained on the seventh, eighth, or ninth post-partum day (Fig. 1). At first it was felt that this was due to the fact that the male babies were circumcised on the seventh or eighth day. But as it occurred with female babies, too, the only common denominator that could be discovered was that the mothers were allowed to be up for the first time on either one of these days.

It was found that approximately one-third of the babies were above birth weight, one-third somewhat below birth weight, while the remaining one-third had just about regained their original birth weight by the tenth post-partum day.

Four groups of patients were chosen to answer the following questions:

1. Will the estrogen, stilbestrol, inhibit the onset of lactation in the nursing human being?
2. Will stilbestrol suppress established lactation in the nursing human being?
3. How useful is stilbestrol in preventing or relieving painful engorgement of the breast in the non-nursing mother?
4. Will stilbestrol prevent painful engorgement in the nursing primiparous mother?

1. In order to observe the effect of stilbestrol upon the initiation of lactation, a group of 25 mothers and babies were chosen in the same manner as the controls. Beginning soon after parturition, varying dosages of stilbestrol, ranging from 50 to 1,000 mg., were administered orally over a course of one to ten days post partum. The babies were allowed to nurse as usual. Briefly summarized, it was found that the onset of lactation on the third or fourth day post partum was not inhibited. It was noted, however, especially when the daily dosage exceeded 15 to 20 mg., that the amount of mother's milk did not reach the average normal range of 8 to 14 ounces daily until two to six days after the stilbestrol had been stopped (Fig. 1). Even with 1,000 mg. (1 Gm.), the secretion of milk was not completely inhibited. In the latter patient, lactation did not become fully established until six days after the last dose of stilbestrol, that is, on the sixteenth day post partum.

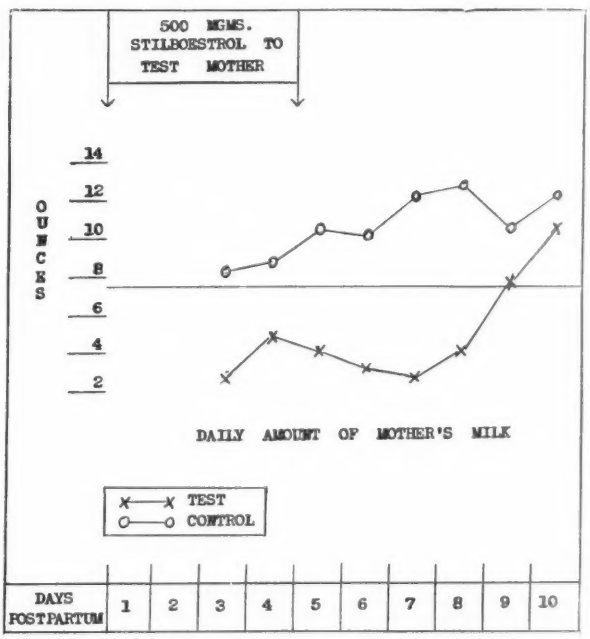

Fig. 1.—The curve of the amount of milk secretion in the control nursing mother compared with that obtained when 500 mg. of stilbestrol was administered orally over the course of four days, beginning soon after parturition. Although the normal onset of lactation was not inhibited, the appearance of the normal average amount of milk secretion was definitely delayed until five days after the last dose of stilbestrol.

From these data, then, it may be said that the estrogen, stilbestrol, will not inhibit the onset of lactation in the nursing human being. It will, however, delay the appearance of the normal average amount of milk secretion. Lactation will be adequately established soon after stilbestrol is discontinued, provided the baby continues to nurse.

2. The effect of stilbestrol upon established lactation in the nursing human being was studied next. Twenty-five mothers were chosen in the same manner as the control group of 50. The babies were allowed to nurse as usual. The test group received varying dosages of stilbestrol ranging from 50 to 500 mg. over a period of two to four days after lactation had been adequately established for twenty-four to seventy-two hours. A minimum of seven and one-half ounces of mother's milk by the fourth day was accepted as normal. In brief, the results obtained demonstrated no apparent suppression of lactation as judged by the baby's daily weight

as well as the amount of milk secretion daily (Fig. 2). Careful pediatric check-up and follow-up revealed no apparent side effects upon the babies.

Clearly, then, the estrogen, stilbestrol, in dosages ranging up to 500 mg. does not affect established lactation in the nursing human being.

3. The efficacy of stilbestrol in preventing or relieving painful engorgement in the non-nursing mother was then determined. One hundred and sixty-five patients formed the basis for this study. For various indications, 100 of these women either did not nurse their babies or else established lactation had to be interrupted. Accordingly, two groups of patients were treated. There were 65 cases in the group where the indication for not nursing was present at the time of delivery. A similar group of 65 patients who were not treated served as controls. (Postabortal cases were not included in this series, since it was found that in the vast majority the degree of painful engorgement was very mild, if it occurred at all, and the amount of lactation, if any, quite slight and transitory.)

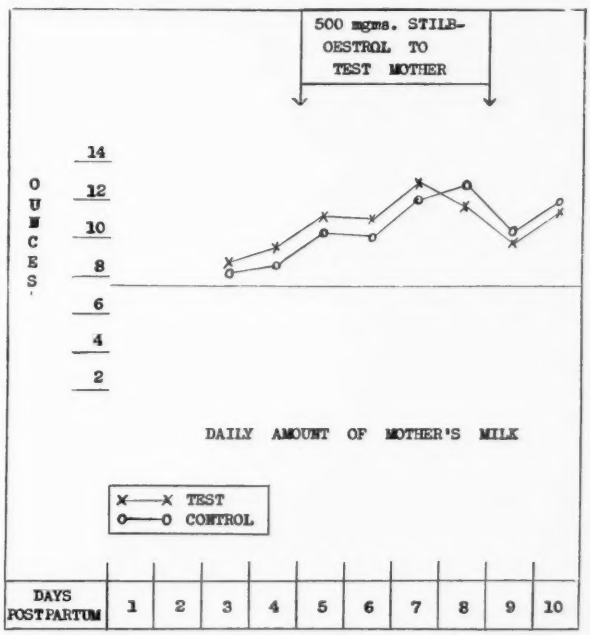

Fig. 2.—Failure of 500 mg. of stilbestrol to affect established lactation in the nursing human being.

After preliminary trials with varying dosages ranging from 10 to 100 mg. over two to ten days, it was found that the most consistent results were obtained with the following schedule. Five milligrams of stilbestrol were given twice the day of delivery and then once a day for three or four days. In multiparas, who gave a history of having lactated well before, the same dosage was continued for five or six days. The total dosage, therefore, ranged from 25 to 40 mg. Fluids were administered freely; in some, they were actually forced. A loose, not tight, uplift binder was used where indicated.

Results were tabulated as excellent if no engorgement occurred, either early or late. The result was classified as good if some mild transitory heaviness or slight filling up of the breasts occurred which could be readily relieved merely by using an adequate *loose* uplift breast binder. The outcome was termed poor if any painful engorgement occurred.

Of these 65 cases, there were 25 patients, or 38.5 per cent, in whom the result could be termed excellent even though in 14 some secretion could be readily ex-

pressed for several days. In 31 cases, or 47.7 per cent, the result was termed good. Of these 31 patients mild, transitory heaviness of the breasts was noted on the second to fourth day in 9 cases. In the other 22 patients, some slight fullness or heaviness of the breasts, associated with a transitory watery-chalky secretion in most of them, was noted anywhere from the fifth to the fourteenth day post partum. The only complaint, if any, was a mild transient heaviness or achiness which was adequately relieved with a proper *loose* uplift breast binder.

In 9 patients, or 13.8 per cent, the results were classified as poor. Analysis of these cases reveals that in 2 of them the pain occurred only in the axillary breast tissue. In another the breasts filled up spontaneously and became painfully engorged on the eighth post-partum day. This patient admitted stripping her nipples because of a slight watery secretion. In 3 others, it was observed that the breast binder had been made so tight that when filling occurred, it went on to painful engorgement of the breasts associated with lumpiness at the region where the binder had cut across the breast. Simple adjustment of the binder frequently gave marked relief.

It is interesting to observe that one of these patients expressed a desire to nurse her baby on the eighth post-partum day. Her breasts, which had remained soft and asymptomatic, were pumped four times and a total of 2 ounces were secured in twenty-four hours. In seventy-two hours, however, her baby was receiving 12 ounces daily from the breast. On the basis of this case, a small series of patients have been treated in the following manner: If, at delivery, an indication is present for the mother not to nurse for the first few days post partum, such as an upper respiratory infection, the mother receives 15 mg. of stilbestrol daily for three to six days. The baby is permitted to suckle when the mother is again well. Lactation soon becomes adequate.

In the control group of 65 patients who did not receive hormonal therapy, severe painful engorgement of the breasts occurred in 31, or 47.7 per cent. Mild engorgement, enough to make the patient complain of fullness or heaviness with occasional secretion of milk, was noted in 29 cases, or 44.6 per cent. Here again a *loose* uplift breast binder was usually sufficient to give adequate relief. In 5 cases, or 7.7 per cent, the patient remained symptomless.

Analysis of these data reveals that about 50 per cent of the control group complained of painfully engorged breasts. With stilbestrol therapy, only 13.8 per cent, or 1 in 7, suffered. In short, the use of stilbestrol had prevented painful engorgement in more than 70 per cent of the patients that would have suffered from it.

There were 35 patients in whom established lactation had to be interrupted for various indications. Stilbestrol was only administered to those patients who had been lactating well up to the time interruption was deemed necessary. If a patient, for example, had fissured nipples because the baby had been suckling mightily on a poorly lactating breast, she was not given hormonal therapy unless actual painful engorgement occurred. Fluids were administered freely; in fact, in many cases they were actually forced. Each received a *loose* uplift breast binder.

Since most of these patients would have been relieved in two or three days on symptomatic therapy, our criterion of a successful result necessarily had to be a strict one. Accordingly, only if practically complete relief was secured within twenty-four hours, was the therapeutic result deemed successful.

The following schedule of dosage was evolved after several preliminary trials. On instituting therapy, 25 mg. of stilbestrol were given at once. The next day two doses of 5 mg. each were followed by 5 mg. daily for three days. Total dosage, therefore, was 50 mg.

Of this group of 35, the results in 30, or 85.7 per cent, were considered as successful. Of the 5 failures, 2 can be ascribed to inadequate dosage. Although the breasts continued to feel lumpy for one or two more days, no pain was noted. In many, secretion was still present anywhere from two days to three weeks later. In 6, a late secondary, slight, painless filling of the breasts, transitory in character, was recorded.

Consequently, when all these results are carefully reviewed, it is found that stilbestrol is, indeed, a rather useful therapeutic agent both in preventing and relieving painful engorgement of the breasts in the non-nursing mother.

4. The usefulness of stilbestrol in preventing painful engorgement in the nursing primiparous mother was then determined, since painful engorgement of the breasts is especially common in this group. Accordingly, 50 primiparas were divided into two groups of 25 each. The test group received 5 mg. of stilbestrol daily for the first three days post partum. In the control group there were 10, or 40 per cent, who suffered from painful engorgement for twenty-four to forty-eight hours, another ten, or 40 per cent, who complained of mild to moderate heaviness, achiness, or tightness of the breasts, while only 5, or 20 per cent, were practically symptom free. In the test group, there were only 2, or 8 per cent, who complained of heaviness and achiness, 2, or 8 per cent, who stated they felt some tightness, and 21, or 84 per cent, whose breasts filled painlessly. The onset of normal lactation was not affected at all.

From these results it is readily seen that stilbestrol is very effective in preventing painful engorgement of the breasts in the nursing primiparous mother, while not interfering noticeably with lactation.

DISCUSSION

Adequate comprehension of the fundamental endocrine physiology of the secretion of milk by the mammary gland necessitates a clear differentiation of the phenomena of the initiation of lactation, the maintenance of established lactation, and the clinical syndrome of painful engorgement of the breasts. Only when this is done may the many seemingly contradictory reports, experimental and clinical, be interpreted correctly.

The initiation of lactation appears to be, basically, hormonal in nature, involving formative stimuli from the ovarian hormones and functional stimuli by lactogenic principles of the anterior lobe of the pituitary. The role played by other endocrine glands, especially the thyroid and adrenal, appears to be secondary, involving water balance as well as nutritional and metabolic factors. It is conceivable, then, that the onset of lactation in the human being might be inhibited by preventing the change in hormonal balance that occurs with parturition. The only substance which yielded any suggestive results was the estrogen stilbestrol.

Although the actual onset of lactation at the usual time was not inhibited by stilbestrol, the appearance of the average normal amount of milk secretion was materially delayed when large doses were given soon after delivery (Fig. 1). Reece and Turner reported similar results with estrogens in the rat.[10] That the onset of lactation might have been completely inhibited if a still larger dosage of stilbestrol had been administered soon after parturition must be considered. On the other hand, similar experiments using 250 mg. of testosterone propionate, 500 mg. of methyl testosterone, 100 mg. of progesterone, and 500 mg. of pregneninolone failed to demonstrate any delay in the appearance of the onset of the average normal amount of milk secretion in the nursing human being.[24]

Most reports have postulated that estrogens inhibit the production of the lactogenic principle(s) of the anterior pituitary and thus inhibit lactation. Turner,[3] however, feels that inhibition of lactation, when it occurs, involves either a direct action upon the epithelium of the mammary gland, or possibly an inhibition of the release of lactogenic hormone from the pituitary, for his group found that treatment with estrogens would markedly raise the lactogenic content of the rat's

pituitary.[25] The former premise seems to be the correct one, for Reece,[26] using colchicine, has shown that injections of estrogen in the rat would bring about an extensive proliferation of the glandular cells of the breasts, as shown by the increased mitotic count. Since a cell that is proliferating cannot very well secrete at the same time, it is assumed that the action of estrogens is a direct one upon the glandular epithelium. Folley and Kon[7] had a similar idea, when they stated that the ability of a substance to inhibit lactation seemed to parallel the proliferating effect of that substance upon the mammary glands.

The hypothesis outlined above seems to explain the effect of large doses of stilbestrol upon the onset of lactation in the nursing human being. The proliferating effect of stilbestrol upon the mammary gland is the same as that of estrone.[27] The apparent cause for the reduced amount of milk secretion during administration of this estrogen becomes discernible (Fig. 1). Since estrogens raise the lactogenic content of the pituitary, whose release seems to be stimulated by the act of suckling,[28] it now becomes clear why, soon after the administration of estrogen is stopped, the amount of milk secretion rapidly becomes normal in the nursing human being.*

The maintenance of lactation involves both hormonal and neurogenic factors. It is a well-known clinical and experimental fact that the secretion of milk will soon cease if suckling, or its equivalent, is stopped. Once lactation is adequately established, relatively massive doses of stilbestrol proved quite ineffectual in suppressing milk secretion in the nursing human being (Fig. 2). Similar negative results have been obtained with 500 mg. of testosterone propionate, 550 mg. of methyl testosterone, 100 mg. of progesterone and 500 mg. of pregneninolone.[24]

The exact mechanism by which the nervous stimulation of nursing maintains lactation is still not clear on the basis of our present knowledge.[3] Suckling appears to be a powerful reflex stimulus for the release of lactogenic hormone from the pituitary, thus maintaining lactation.[28] The centrifugal arm of this reflex directly involves the nerves leading to the spinal cord, for denervation of all the exposed breasts by a spinal cord lesion leads to rapid cessation of milk secretion even if the young continue to nurse.[29] The centripetal arm of this reflex is hormonal, for denervated or transplanted mammary glands will continued to lactate provided a normal breast of that animal is stimulated to secrete by suckling.[30]

The act of nursing, then, seems to be a much more powerful stimulus for the secretion of milk by the glandular epithelium of the breast than 500 mg. of stilbestrol is a stimulus for proliferation of this same epithelium. This explains why established lactation may be maintained in several species, including man, through successive pregnancies.

*Recently, Folley, Watson and Bottomley (J. Physiol. 98: 15, 1940) reported that they were able to stimulate the appearance of lactation in 2 virgin goats by combining local application of stilbestrol with mechanical massage of the mammary gland. Somewhat similar observations were noted in these studies in a patient whose breasts had never filled, much less lactated, after four previous full-term pregnancies. She received 50 mg. of stilbestrol during the first two post-partum days. The baby was put to breast. On the fourth day, her breasts became engorged for the first time in her life. Milk secretion soon appeared, but proved to be inadequate, totalling 2 to 3 ounces daily. This evidence, however, is only suggestive, being far from conclusive.

Painful engorgement of the breast is caused by lymphatic and venous stasis, not by distention of the ducts with milk.[23] Unfortunately, most of the clinical reports on the effect of estrogens upon lactation in the human being have confused painful engorgement with the onset of lactation, using these terms interchangeably. These are two distinct and separate phenomena. By what means painful engorgement is prevented or relieved by the various sexual hormones cannot be explained on our present-day knowledge. That it is not by inhibition of lactation is obvious from the fact that lactation may proceed normally as in the nursing primiparous mothers treated with stilbestrol. A similar finding has been reported with testosterone propionate.[31]

The delayed filling of the breasts and secretion therefrom that was noted in some of the non-nursing group may be explained in the following manner: The administration of estrogen brought about an increased lactogen content of the pituitary. After the stilbestrol was stopped, the lactogenic hormone was now free to act upon a breast already suitably prepared by the previous pregnancy.

An illustrative case is that of the mother who received stilbestrol after the baby was removed from the breast because of fissured nipples. Six days later her breasts began to fill up again. A second course of stilbestrol was given. Seven days later her breasts again filled up and ran over with milklike secretion.

The results obtained with stilbestrol orally in preventing painful engorgement of the breasts in the nonnursing mother are quite similar to those reported with 10 to 25 mg. of estradiol benzoate given intramuscularly in oil.[18, 19] With stilbestrol, the result was termed excellent in 38.5 per cent as compared to 29 per cent[18] and 32 per cent[19] when estradiol benzoate was used. With the latter estrogen failures occurred in 14 per cent[18] and 9 per cent,[19] while with stilbestrol 13.8 per cent failed to respond. The advantages, then, lie with stilbestrol for two reasons: First, it is active orally, requiring a minimum of nursing care. Second, the cost of stilbestrol is extremely little compared to that of the natural estrogen. The only disadvantage of the estrogens, it seems, is the late secondary filling that so frequently occurs. This may be obviated to a great extent by using an adequate uplift breast binder that is *loose*, not tight. A second course of stilbestrol is rarely, if ever, necessary.

COMMENT

Stilbestrol has been reported to have so-called "toxic" effects in the nonpregnant individual.[32] Two puerperal patients were given 1500 mg. (1.5 Gm.) during the course of ten and twelve days, respectively. Complete blood chemistries, urine examinations, blood counts, etc., before, during, and after the administration of this enormous dose failed to reveal any "toxic" effects. One patient felt slightly dizzy for about thirty minutes after a dose of 50 mg. Pre-eclamptic and eclamptic patients with uric acid values between 7 and 9 were given as much as 150 mg. of stilbestrol in the space of twenty-four hours for inducing labor with no untoward effects. Presumably the pregnant and puerperal patient can metabolize stilbestrol more efficiently than the nonpregnant one.

SUMMARY

The synthetic estrogen, stilbestrol, when administered orally soon after parturition in dosages up to 1,000 mg. did not inhibit the actual onset of lactation in the nursing human being. The appearance of the average normal amount of milk secretion, however, was delayed until as many as five or six days after the last dose of stilbestrol.

No effect at all was noted upon established lactation in the nursing human being with 50 to 500 mg. of stilbestrol administered orally in divided doses over a period of one to four days.

In the prevention of painful engorgement of the breast in 65 non-nursing full-term mothers, 25 to 40 mg. of stilbestrol orally in divided doses failed to yield a satisfactory result in but 9, or 13.8 per cent. On the other hand, in a control group of 65 similar cases, 31, or 47.7 per cent, suffered from painful engorgement of the breasts.

In 35 cases where adequate established lactation had to be interrupted, 50 mg. of stilbestrol orally in divided doses provided satisfactory relief for painful engorgement within twenty-four hours in 30, or 85.7 per cent.

Of 25 primiparous nursing mothers given 5 mg. of stilbestrol daily for the first three post-partum days, practically painless and asymptomatic filling of the breasts occurred in 21, or 84 per cent. In the control group, however, only 5, or 20 per cent, had painless filling of the breasts.

The pregnant and puerperal patient was found to be unusually tolerant of huge doses of stilbestrol.

The authors gratefully acknowledge the sincere interest of Dr. Harry Aranow during the course of these studies. In addition, the splendid cooperation of the Misses Andes, White, and Mills of the nursing staff of the Obstetrical Division was deeply appreciated.

The stilbestrol used in this study was kindly supplied by Dr. J. A. Morrell of E. R. Squibb & Sons.

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Harlem Hospital
1882 Grand Concourse

PROLAPSE AND TORSION OF THE RIGHT FALLOPIAN TUBE WITH VAGINAL BLEEDING, FOLLOWING VAGINAL HYSTERECTOMY

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THE following case presents an unusual complication following vaginal hysterectomy: prolapse of the fimbriated extremity of the right Fallopian tube through the drainage site at the apex of the vaginal vault, torsion of the tube, and intermittent bleeding from the fimbriated ostium.

Mrs. A. M. W., aged 25 years, housewife, was seen by one of us for the first time on Aug. 20, 1939. She had had periumbilical pain and profuse diarrhea for two days. Both responded to paregoric and her symptoms subsided completely in twenty-four hours. She was asked to return for more thorough study because of the following history:

Her menses had begun at 14 years of age, occurring irregularly every two to three weeks, lasting six to nine days, with severe hypogastric cramps beginning one week before and continuing through the entire period. Previous operations were a tonsillectomy at eight years of age and an appendectomy with drainage at the age of seventeen. She was married late in 1935 and had one child in June, 1936.

She was hospitalized on Jan. 31, 1938, complaining of pain in the left inguinal region before and during periods and the passage of clots at the menses with relief. Her pain was very severe for eleven months before admission. The period occurring from Jan. 25 to 30, 1938, was the shortest of her experience.

Physical examination revealed markedly carious teeth and a few apical râles bilaterally; pelvic examination demonstrated a small introitus, good perineal support, normal vagina, small cervical scar, first degree prolapse of the uterus with marked retroversion and a fullness in the left adnexal region. Urinalysis, negative; hemoglobin, 85 per cent; erythrocytes, 4.4; leucocytes, 9,000; differential, normal; sedimentation rate, normal.

A diagnosis of obstructive dysmenorrhea and ovarian menorrhagia was made and on Feb. 2, 1938, under gas-ether anesthesia, a dilatation and curettage and right oophorectomy were performed. The right ovary was cystic, but the left adnexa and uterus were normal. No pathologic diagnosis of the endometrium was made. She was discharged Feb. 13, 1938, with a slightly elevated temperature, 99° F.

Readmissions.—On April 4 to April 11, 1938, she re-entered the hospital complaining of frequent menses and menorrhagia. She had menstruated from February 19 to 27 with less pain than preoperatively; from March 2 to 11, 1938, and from March 24 to April 2, 1938. Left inguinal tenderness was present. Urine, blood count, and sedimentation rate were normal. Temperature was 99.2° F.

From May 16 to May 22, 1938, she again was hospitalized, complaining of periumbilical cramps, bleeding every thirteen days for seven days, and dysmenorrhea. Urine and sedimentation rate were normal; hemoglobin, 75 per cent; erythrocytes, 4.1; temperature was normal except for two days when it was over 99° F.

On Aug. 15 to Sept. 2, 1938, she complained of menorrhagia and metrorrhagia. An x-ray of the chest showed inactive apical tuberculosis; basal metabolic rate, plus 4; Wassermann and Kahn reactions, negative; hemoglobin, 76 per cent. On Aug. 16, 1938, a vaginal hysterectomy was performed; a cigarette drain was removed in forty-eight hours. Pathologic report stated that the uterus had atrophic mucosa, an

eroded cervix and corporal fibrosis. When discharged, her temperature was normal, and there was no bleeding.

In October, 1938, she bled slightly, and in November severe bleeding occurred. This was repeated at least bimonthly for one to six days, and was associated with pain in the lower left abdomen. She was given various forms of hormone and snake venom therapy with no relief.

Her last bleeding seemed to occur suddenly and lasted from Aug. 21 to Aug. 23, 1939. On Aug. 24, 1939, physical examination revealed a loss of 35 pounds in weight. At the apex of the vaginal vault we found a small nodular mass about 1 cm. in diameter which appeared edematous and seemed to be covered with small papillary projections (Fig. 1). A diagnosis of endometrioma of the vaginal vault was made. She was re-examined on Aug. 26, 1939, by one of us who thought the vaginal mass was a polyp. (At the time we were under the impression that her tubes had been removed as well as the uterus.)

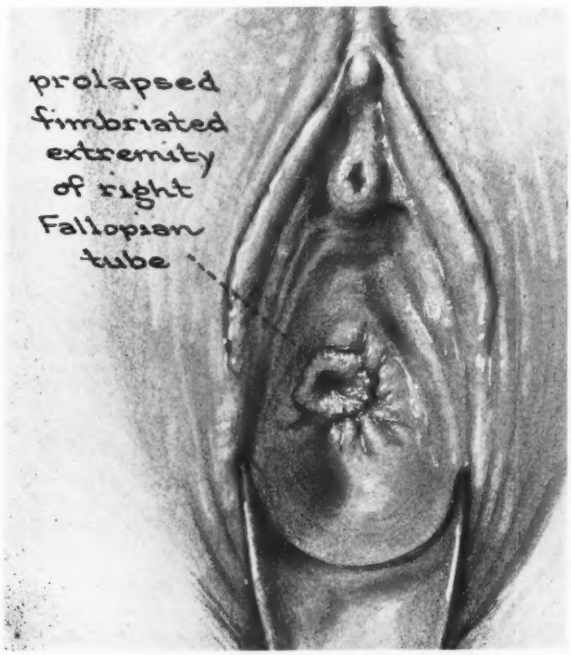

Fig. 1.—Mass covered with papillary projections at apex of the vaginal vault.

She entered the hospital on Aug. 27, 1939 (hemoglobin, 90 per cent; erythrocytes, 4.55; leucocytes, 4,800; differential, normal), and was operated upon the following day. Through the vagina, a portion of the mass was grasped with a tenaculum. The operator was unable to loosen it, so a piece was excised for tissue study.

Because of the possibility of a prolapsed tube, the abdomen was opened through a midline infraumbilical incision. The left ovary was cystic and badly degenerated. A cyst of Morgagni was present on the right side. The fimbriated end of the right tube was found to disappear into the vaginal vault; it was pulled up and a bilateral salpingectomy and right oophorectomy were done (Fig. 2). The two leaves of the broad ligament were drawn together over the opening in the vaginal dome. The abdomen was closed in layers without drainage. Convalescence was uneventful, and she was discharged on Sept. 5, 1939.

Pathologic Report.—Left ovary was 3 cm. in diameter, and there were multiple cysts with degeneration. Both tubes were degenerated. The right tube contained

a cyst of Morgagni 1 cm. in diameter. The right tube was edematous and the villi hypertrophied; there was extreme congestion and edema of the walls of the blood vessels with old and new thrombi and cellular infiltration. The stroma contained areas of hyalinization. There was no evidence of ectopic endometrium (Fig. 3).

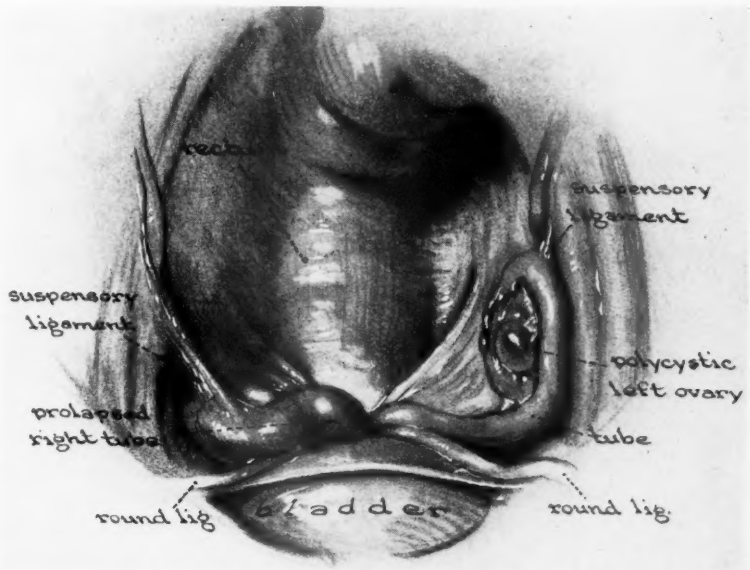

Fig. 2.—Visualization of fimbriated end of right tube disappearing into vaginal vault. Right ovary had been removed previously. Left ovary cystic and badly degenerated.

Fig. 3.—Microscopic section (×80) of right Fallopian tube showing hypertrophy of villi, congestion, edema of the walls of the blood vessels with old and new thrombi and cellular infiltration. The supporting stroma contains areas of hyalinization.

Diagnosis.—Torsion of Fallopian tube.

At patient's last visit (Oct. 22, 1940), she stated that there was neither bleeding nor vaginal discharge. She had gained 27 pounds. Flushes were controlled effectively by the use of estrogenic hormones.

COMMENT

It is reasonable to assume that the cigarette drain, which was removed forty-eight hours after the vaginal hysterectomy, offered the hiatus through which the fimbriated extremity of the right Fallopian tube prolapsed. It is also possible that the fimbriae might have become adherent to the gauze of the drain and been inadvertently pulled through the hiatus when the drain was removed. Torsion of the structure then occurred with resultant edema, venous congestion and hemorrhage. Whether or not endocrine imbalance added to this mechanical derangement with resultant periodicity of bleeding, we are unable to say.

COBRA VENOM FOR INTRACTABLE PAIN

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BECAUSE of the long-continued intractable pain associated with incurable pelvic cancer, and the disappointing results of the anodyne measures usually employed, morphine addiction, nausea, vomiting, insomnia, and euphoria so frequently seen making the use of these analgesic measures unsatisfactory, the author decided to try cobra venom for the relief of pain.

Cobra venom was studied by Dr. Adolph Monae-Lesser in 1929. He observed the relief of pain in a Cuban leper who was bitten by a tropical spider. This experience caused him to study the action of cobra venom. Dr. David I. Macht deserves the credit for a greater part of the physiologic and pharmacologic data which have been obtained from work done in the United States. He has proved conclusively that the venom, like morphine, has its effect on the higher centers of the brain and has no peripheral action at all. Dr. Macht has likewise carried on a biochemical investigation in which he has established the fact that opium derivatives are oxidized from the brain very rapidly, while the venom from the cobra is found unchanged in fresh brain tissue for a much longer period of time. This explains its tardy action and its prolonged anodyne effect in contradistinction to morphine. The latter produces rapid analgesia, but unfortunately the effect is not very lasting. Fortunately cobra venom is not habit forming. In other words, a patient is not likely to become addicted to a drug from which he obtains no relief for seventy-two hours after administration.

On the basis of experimental clinical observations made by Dr. Macht and others, I have used this drug on 18 patients, 15 of whom were considered hopeless.

CASE REPORTS

A. T., 57 years of age, had a Group IV carcinoma of the cervix and received 7,200 r. units of x-ray. After temporary improvement she developed pain and continued bleeding. Cobra venom was started in August, 1939, by Dr. C. W. Ohl, of Chickasha, Oklahoma. Her malignancy advanced and she continued to bleed on repeated occasions, but in spite of this she has gained weight and has been relieved of pain. This patient continued to be comfortable on 5 mouse units, or 1 c.c. of the cobra venom every third day.

T. L. W., 50 years of age, Group III cervical cancer, received x-ray and radium, but after eight months the growth began to progress rapidly and she developed unbearable pain. Cobra venom was begun in August, 1939, under the supervision

of Dr. C. M. Cochran, Okemah, Oklahoma. Though quantities of anodyne pills had been given, she experienced little relief from pain until cobra venom was administered. The control of pain was almost 100 per cent. Although she continued to lose weight, she gained in strength and well-being.

O. D., 65 years of age, Group III carcinoma of the cervix, had a pathologic fracture through the neck of the left femur and has obtained 100 per cent relief from her pain since the use of the venom, which has been given by Dr. L. R. Wilhite, of Perkins, Oklahoma. Her fracture has united, there is no evidence of bone destruction, and at the present time she takes 5 units weekly and is without pain.

N. J., 40 years of age, had a Group III carcinoma of the cervix, received radium and x-ray, but a year later began to have severe pain. She was given cobra venom by Dr. D. B. Collins, of Waurika, Oklahoma. He thought she was obtaining relief from the injections, but later learned that she was taking papine for control of pain. It is interesting to note that she did eat well and gained weight after the venom was started, whereas she had lost fourteen pounds in the previous two months. The patient died of a pulmonary embolus. She is reported here as obtaining no relief from the use of the venom.

E. N., 44 years of age, Group III cervical malignancy, was bedfast because of pain, anorexia, nausea, and vomiting from the use of aspirin. After two months' routine administration of cobra venom she gained weight and reported 85 per cent relief from pain. She found it unnecessary to continue its use, but after eight weeks she again began its administration and obtained satisfactory relief on an ampoule every third day.

M. B., 53 years of age, Group II cervical malignancy, had an extension into the vesicovaginal area which caused severe pain. Cobra venom given by Drs. Cotton and Van Matier, of Walters, Oklahoma, afforded complete relief after the sixth injection. The attending physicians confirm the above report and state that all opiates were discontinued, and after two months have found it unnecessary to continue with the drug.

L. N., 39 years of age, had a cervical stump malignancy, Group IV, with metastasis into the bladder. After six daily injections of cobra venom, she was just as comfortable on ⅛ gr. of morphine sulfate as she had been on ¼ gr. She was difficult to control and insisted upon leaving the hospital. Since it was impossible to evaluate results, she is reported as receiving no relief.

I. M. O., 32-year-old negro woman, carcinoma of the cervix, Group III, received the maximum amount of x-ray and radium. In spite of this, she was losing weight at the rate of 7 pounds a week because of constant, severe pain in her pelvis. After three injections of the venom she became comfortable, although the pain had previously required large doses of morphine. Her injections have been gradually reduced in frequency, and she is now receiving 5 units every sixth day, remaining absolutely free of pain. There is a weight gain of 35 pounds. During the course of her treatment she developed huge bluish spots on her tongue and gums, and a few small petechial-like areas in her hands. These were not accompanied by pain and have gradually faded away.

M. C., 38-year-old negro woman, Group III carcinoma of the cervix, was given palliative x-ray last July. Her malignancy progressed and with it she developed severe pain. Although this patient died, the doctor in whose home she worked advised us that she obtained complete relief after the fourth dose of cobra venom.

D. M. D., Group III carcinoma of the cervix, in spite of a series of x-ray treatments developed severe pain. She was given cobra venom by Dr. A. E. Berry, of Mountain View, Oklahoma, without any apparent relief. However, she has been in the hospital since and at the end of a week had not asked for so much as an aspirin; nevertheless she insists her pain is severe. She is being reported as obtaining no relief.

M. E., 40-year-old woman, had a hysterectomy in 1928 and now has a carcinoma of the cervical stump, Group III. Her response to treatment one year ago was gratifying, but she suddenly developed an extensive recurrence, having severe pain in the right thigh, with contracture. Her x-ray was negative for bone metastasis,

and she was admitted for intrathecal alcoholic injections, which were done on two different occasions without relief. She was then given cobra venom and obtained complete relief, in spite of a rapid development of a huge mass in the right side of the abdomen. Following the relief of pain the contracture responded to diathermy and massage.

V. W., a 62-year-old woman, had severe pain sixteen months after treatment for an advanced, Group III, undifferentiated malignancy of the cervix and body of the uterus. She was given cobra venom by Dr. C. E. Northcutt, of Ponca City, Oklahoma, and he reports that she obtained most satisfactory results, and that it was unnecessary for her to use any other drugs for the relief of pain.

B. L., a 37-year-old woman who had a Group IV carcinoma of the cervical stump, obtained no regression from x-ray series. As the growth continued she developed pain, requiring morphine for relief. She was given cobra venom with no appreciable relief. Two alcoholic injections were then given into the spinal canal, with relief for twenty-four hours following the first, and sixteen hours following the second. She is now up and about following a bilateral chordotomy and is completely free of her pelvic pain. This patient is being reported as obtaining no relief from cobra venom.

M. H., a 33-year-old white woman, had a Group IV carcinoma of the cervix. She was given palliative x-ray following which her pain became unbearable and necessitated opiates. She was started on cobra venom and reported her first night's sleep after the fourth dose had been administered. Her relief is estimated as being at least 85 per cent.

M. L., 57-year-old colored woman, was apparently cured with x-ray and radium of a Group III carcinoma of the cervix in 1937. During this time she became addicted to morphine and has taken one-fourth grain four times daily since. A few weeks ago she was brought into the hospital and was taken off the morphine and put on cobra venom. A short time later a vesicovaginal fistula was closed. Patient remained comfortable postoperatively on cobra venom and phenobarbital. When dismissed, she was taking one ampoule every third day.

Encouraged by the results obtained in the relief of pain in pelvic malignancies, I decided to try the remedy in the following cases:

Mrs. H., a nurse's mother, aged 63 years, who was a hopeless cripple from arthritis, was given cobra venom by her daughter and after two days of practically complete relief suddenly took seriously ill with a severe bronchitis. By the time she had recovered from her upper respiratory infection, in spite of the fact she had received her venom every other day, she again developed the pain in her joints and asked that the medication be discontinued. It was discontinued after it had been given twice daily for four consecutive days without further relief.

Mrs. E. H., a doctor's widow, had had diverticulosis of the colon for many years and now had a malignancy of the rectum and lower sigmoid, with constant pain. She vomits after the administration of morphine but can tolerate small doses of hyoscine, morphine, and cactoid compound. She has taken 20 ampoules of cobra venom in a span of fourteen days without any apparent relief.

L. S., a 14-year-old childbirth injury case, with severe pain from muscle spasm, was given 20 ampoules of cobra venom, sometimes receiving two at a time. She received no relief whatsoever and required her same huge doses of barbiturates as before.

The above brief case reports seem to warrant a continued trial of this therapeutic agent. The cobra venom is supplied in 1 c.c. ampoules, each representing 5 mouse units. It was given intramuscularly. The initial dose was ½ c.c., with succeeding daily doses of 1 c.c. until relief was obtained, or until 10 ampoules were given. It should be noted that in 12 of the cases reported the estimated relief of pain ranged from 85 to 100 per cent. While there were no serious untoward sequelae, there were definite local and systemic reactions encountered, manifested by

transitory shock and cerebrovascular disturbances. The use of cobra venom should be limited to carefully chosen cases and its effects closely observed until its physiologic action is better known to the clinician and its ultimate results more clearly defined.

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PREGNANCY COMPLICATED BY TUBOOVARIAN ABSCESS

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THE early diagnosis of pregnancy has been greatly facilitated by the Aschheim-Zondek test. A negative following a positive test would indicate death of the fetus. The following case report demonstrates such findings complicated by the development of a large abdominal tumor.

Mrs. N., married, aged 22 years, primipara, consulted me Sept. 23, 1938. Her last regular menstrual period began July 5, 1938. On August 1 she had had a light menstrual flow lasting two days. Starting again August 27 she continued to flow for seventeen days, using 4 to 6 pads daily. An Aschheim-Zondek test which had been made September 10 was positive.

Family history revealed three cases of tuberculosis, no diabetes or cancer. Menses began at 12 years of age, regular, twenty-one-day cycle, lasting six days, moderate flow, no clots or leucorrhea, slight pain. An appendectomy for ruptured appendix was done in 1925.

General health had been poor for eight or nine years. As an adolescent she had had various attacks of cystitis and at one time nephritis with albumin. Examination had revealed a pelvic tumor but her father would not permit an operation.

During the past year she had been treated for achlorhydria, retroverted uterus by pessaries, and had been given thyroid for weakness and fatigue. She had been troubled with headaches, vertigo, blurring of vision, and poor appetite. She had palpitations and was very nervous and tired easily. At times she would be quite nauseated. She complained of "soreness in ovaries," indigestion, and constipation.

Physical examination in my office Sept. 23, 1938, revealed a nervous, tall, pale, asthenic individual, appearing to be about 30 years of age, weight 112 pounds (average weight 145), temperature 98.6° F., pulse 80, respiration 20. Other findings

were irrelevant except for pelvic and abdominal findings. The Mantoux test gave a positive reaction but the chest x-ray was negative.

Pelvic examination revealed an anteverted uterus, globular in shape and enlarged to approximately a three months' pregnancy. The isthmus and cervix were soft. Uterus was moderately fixed and pressure caused considerable pain.

On October 2 she had a menstrual period at the regular time and passed some large blood clots but no tissue that looked like placenta. Because of the bleeding, cramps, and lower abdominal pain, it seemed that an abortion was imminent. In an effort to prevent this she was given triweekly doses of antuitrin-S and corpus luteum. Bromides and vitamin B were given to relieve nausea and ⅙ gr. of morphine sulphate orally for pain as necessary.

Her blood Wassermann on October 10 was negative. Blood count was as follows: Hb 70 per cent; red blood count, 3,260,000; white blood count, 21,800; polymorphonuclear neutrophiles, 80 per cent; basophiles, 1 per cent; small leucocytes, 16 per cent; staff cells, 2 per cent; color index, 1. Urine was negative. Vaginal slide was negative for trichomonas or gonorrhea. Basal metabolism was minus 22.

By October 24 her pain had become more severe and rectal palpation revealed cervical dilatation of approximately 1½ cm. and 40 per cent effacement. We were unable to understand why she did not abort. Because of the pain she was hospitalized and consultation held.

On November 10 there was less pain and the smooth outline of the fundus was less tense. Our plan was to let her abort naturally. In order to build up her general condition she was given a transfusion of 500 c.c. of citrated blood followed by another on November 15. Her temperature and pulse remained normal. On November 16 she was improved and left the hospital, her hemoglobin being 88 per cent, red count 4,640,000, and white and differential normal.

By November 18 the patient had noted no movement. The fundus was palpable above the umbilicus. An x-ray showed no fetal structures. In addition to the abdominal cramps, she had now developed severe cramps in both legs and severe pain in the right groin. Rectal examination gave the impression of a 3 cm. dilated cervix inside of which was a bulging fluid-like mass, smooth in outline. The fundus was very tense and felt like a tonic uterus.

On November 25 the patient felt that the fundus was getting smaller and on examination it did prove to be 4 cm. below the umbilicus and the mass was soft except for a nodule at the right of the linea alba just above the symphysis about 6 to 8 cm. in diameter. The laboratory report was hemoglobin 100 per cent; red cells, 4,180,000. Serum calcium was 10 mg. and blood phosphate 3.5 mg. per 100 c.c. of whole blood.

After decreasing in size the fundus again enlarged. Leg cramps, numbness, and lower abdominal pain increased in severity so that codeine sulphate was necessary to relieve pain. On December 9 she had a slight bloody show and severe pain which did not simulate uterine contractions. The feet were swollen and the patient weighed only 112 pounds. Abdominal examination showed the presence of a hard tumor as before described, and a laparotomy was decided upon. Consultant considered the tumor mass to be a fibroid of the uterus with a cystic mass related to a pelvic organ but extrauterine.

On December 10, the patient was given 500 c.c. of citrated blood. Salpingograms made before the operation revealed a large soft tissue extrauterine tumor. Laparotomy was performed December 12 and was followed by another injection of 500 c.c. of citrated blood.

Operation.—Bilateral salpingectomy and oophorectomy.

Findings.—There was a large firm tumor mass extending in the midline above the umbilicus containing a clear yellowish gelatinous material in the upper portion. The uterus was pushed far down in the right side of the pelvis. The mass was found to have its origin in the left tube and ovary. The right tube and ovary were bound up in a tight mass about 6 by 8 cm. in diameter.

The abdomen was opened through a suprapubic midline incision. By careful blunt and sharp dissection the mass was freed in all portions except deep poste-

riorly. When gentle traction was placed upon the cyst, it ruptured and was found to contain perhaps 1,500 c.c. of greenish foul pus. The cystic mass was removed leaving a thick wall of granulation tissue. The uterus was identified; the right tube and ovary were removed except for a portion of the ovary which was left attached to the tuboovarian ligament. A portion of the cyst cavity was obliterated with sutures of plain catgut. Four cigarette drains were placed into the pelvis, and the abdominal wall was closed in layers.

Pathologic Report.—Dec. 12, 1938: Specimen consisted of the wall of a cyst which had measured approximately 12 to 15 cm. in diameter. The lining was plastered with masses of coagulated purulent-appearing exudate, and beneath the exudate the lining membrane of the cyst presented a papillomatous appearance; the surface had a velvety appearance and was covered with many small papillomas ½ to 1 mm. in diameter. The outer wall was thickened and fibrous and revealed many adhesions.

A second mass 6 cm. in diameter revealed a further cystic growth, apparently a Fallopian tube. The lumen was distended and the mucosa revealed a yellowish pigmentation.

Microscopic sections through the wall of the cyst revealed inflammatory infiltration throughout all areas. There was a papillary proliferation of the lining membrane characterized by a rather dense fibrous stroma and continuation of dense inflammatory changes in several areas. Sections through the wall of the cyst revealed infiltration of large deeply-staining cells apparently originating from the lining epithelium of the cyst cells extending outward into the wall of the cyst and scattered in small masses and clumps through the tissue interstices. The picture was not definitely that of malignant growth. Further study of paraffin sections reveals no evidence of any malignancy.

Diagnosis.—Papillary cystadenoma of the ovary with marked inflammatory changes; salpingitis.

The pus was cultured and a guinea pig was injected to rule out an acid fast organism as the cause of such a low grade inflammatory process but the tests were negative.

Laboratory Report.—Smear and culture of light green pus obtained from right Fallopian tube and amber colored fluid from left tube: Gram's stain: Slide was loaded with disintegrating pus cells. There were gram-positive diplococci, sometimes almost bacillary in form, often seen in chains. Bacteria did not stain typically and appeared to be partly dissolved. Seventy-two-hour culture, no bacteria found. Acid fast smear for tuberculosis, none found.

Direct smear from right tube revealed many leucocytes and a few gram-negative bacilli. Cultures seventy-two hours, no bacteria found.

Progress.—There was a profuse serosanguineous drainage for four days. The postoperative condition was good until December 14 when the patient became quite toxic and had a white blood count of 49,500, a differential count of small lymphocytes 4 per cent, large mononuclears 2 per cent, neutrophiles 93 per cent, eosinophiles 1 per cent, staff cells 12 per cent, and vacuolated cells 2 per cent. She was given another 500 c.c. of citrated blood and from then on the blood count and temperature dropped. She was afebrile after the fourth postoperative day and the white count dropped to 19,500 on the sixth, and to 14,900 on the twelfth postoperative day when she was discharged from the hospital. The wound drained a bloody fluid for ten days and then gradually the drainage became serous and the wound was entirely healed by February 3. Her weight had increased from 95 pounds to 107 during this period.

The pelvic wall of plastic exudate surrounding the pyosalpinx was gradually absorbed until the abdomen became soft and normal to palpation. Six weeks after the operation pelvic examination revealed an anteverted, moderately fixed uterus with no parametrial tenderness. The cervix was clean. After two months she had ovarian deficiency symptoms necessitating estrogenic hormone injections. One milligram tablet of stilbestrol daily also relieved her of the hot flushes.

SUMMARY

This case has been reported because of the unusual size of the left tube and ovary. One may be criticized for the time element in waiting for surgical intervention, but again the time element may have saved her life by allowing nature to wall off securely and immunize the peritoneal cavity against the invading organism. The cul-de-sac could have been needled and the pus evacuated through the vagina; however, the afebrile course gave no indication of a purulent process.

410 Arts Building

PREGNANCY AND FEVER THERAPY

Johann R. Marx, M.D., Ingleside, Neb.
(From the Hastings State Hospital)

THE following case is presented because of a successfully tolerated pregnancy during the full course of artificial fever therapy for general paresis.

Mrs. G. M., a white, 36-year-old, married female had been essentially well until approximately ten years ago at which time a positive blood Wassermann revealed syphilis. There was no history of primary or secondary syphilitic lesions. She had received regular treatment with arsenicals and heavy metals ever since. The blood serology changed frequently from positive to negative during the course of the years but remained positive for the last two years despite all chemotherapy. She gave birth to four children whose cord blood was checked for syphilis at the time of delivery and found to be negative, except in the last child which is now one year old. There was no history of abortions or miscarriages.

During the last six months the patient became increasingly forgetful, careless about her appearance and conduct, exhibited bewilderment, and complained of headaches. She experienced difficulties when walking in the dark, and complained of occasional momentary periods of blindness. Immediately before admission to this hospital in September, 1939, she had received three fever treatments in a private hospital.

The examination on admission showed typical mental and physical symptoms indicative of general paresis which diagnosis was confirmed by positive blood and spinal serology and paretic gold curve.

On Oct. 6, 1939, the patient was started on artificial fever therapy in the Kettering Hypertherm. The first three treatments of five hours at a temperature of 105° F. to 106° F. once weekly, were satisfactorily tolerated. The patient was extremely cooperative, and there were no complications with the exception of some nausea. During the fourth treatment, the patient complained of pain and cramps in her abdomen. These, however, disappeared at the end of the treatment. During the following two treatments, the patient's nausea increased considerably; she experienced repeated voluminous emesis. A physical examination at that time revealed the presence of a pregnancy of approximately three months' duration. It was impossible to obtain any reliable data from the patient about her last menstrual period. Although pregnancy is considered as a contraindication to fever therapy, it was decided to continue the patient's course with increased precautions. The length of the treatments was shortened to three hours and thiamine chloride was administered intravenously.* The treatments under that regime were tolerated much easier than the previous ones, and the nausea and emesis disappeared almost completely. During a few of the treatments, the patient exhibited mild symptoms of tetany which were successfully remedied by maintaining the patient on an increased calcium-gluconate medication.

*20 mg. "crysto-vibex" during the fever and the two preceding days.

In combination with the fever treatments the patient received mapharsen and bismuth salicylate which were continued after the termination of the fever. The pregnancy continued without any difficulties while the patient completed fifty hours of fever in thirteen treatments. A serology check in March, 1940, showed essentially the same findings as before the fever therapy, except that the spinal Wassermann changed from a strong positive to a weak positive. The patient's mental and physical condition showed no remarkable changes except for improvement in walking.

On April 15, 1940, the patient gave birth to a living boy in a quick and uncomplicated delivery. The child weighed 7 pounds 8 ounces and showed no physical abnormalities. The Wassermann determination on the cord blood of this child returned negative.

The case appears instructive because a full course of artificial fever therapy was completed on a pregnant woman without any ill effects to the pregnancy or mother. The intravenous administration of thiamine chloride appeared useful in relieving hyperemesis. It may be considered a result of the combined fever and chemotherapy that the child's Wassermann was negative, while the preceding child had been afflicted with congenital syphilis despite continuous chemotherapy of the mother during pregnancy.

SUMMARY

A case of general paresis is presented in which artificial fever treatment was carried out successfully without interference with an existing pregnancy.

The child showed no signs of physical damage from either fever therapy or syphilis. Its cord blood Wassermann was negative despite positive blood and spinal serology of the mother.

OBSTRUCTED LABOR DUE TO FETAL ASCITES

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(From The Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine)

THE following case of fetal ascites is reported because of the rarity of this condition and because certain of the mother's prenatal physical findings suggested abnormal uterine contents.

Mrs. L. L., aged 21 years, weight 154 pounds, primipara, entered the hospital approximately five weeks before term, with chief complaint of aching in the side and back, associated with dysuria. The pregnancy had been uneventful until five weeks previously. Forty-eight hours before admission she had a chill. Examination on admission revealed left costovertebral tenderness; uterus was the size of a seven and a half months' pregnancy, with position L.O.A., head floating. Temperature was 101.2° F. Urinalysis showed numerous clumped white blood cells, 3-plus albumin, and bacteria; when cultured, the bacteria proved to be *B. coli communis*. The blood showed 8.2 Gm. hemoglobin and 3,100,000 red blood cells. Wassermann was negative.

The treatment consisted of multiple transfusions, forcing of fluids and acidification of urine. She was discharged, improved, ten days after admission. She reentered the hospital two weeks later, two weeks from term, with a history of leaking a small amount of amniotic fluid. Examination at this time revealed a striking enlargement of the uterus over that found on previous examination. She continued to leak fluid slowly for two days and then went into active labor, with crowning of the fetal head in ten hours. The head was delivered with low forceps after an episiotomy. The shoulders seemed to be caught tightly by what was known to be

an adequate pelvis. It proved necessary to do a bilateral cleidotomy which quickly facilitated the delivery of the shoulders. After the shoulders and head had been delivered and the amniotic fluid drained off, examination showed that there was still a large abdominal tumor. This tumor prevented the extraction of the fetus. An attempt to enter the uterus with the gloved hand and arm was quite difficult, but was accomplished by partially crushing the chest of the dead fetus. A large fetal abdomen was felt. This was punctured with Smellie's scissors and a large amount of clear yellow fluid containing some fibrin flakes drained out. The fetus then delivered spontaneously. After the placenta had been delivered and the episiotomy repaired, the fetal abdomen was examined through an incision. The bladder, intestines, and liver were grossly normal; the kidneys were abnormally small, measuring not over 3 cm. in length.

The postoperative course was complicated by three chills, the only objective findings being a tender uterus. Treatment consisted of oxytocics and blood transfusions. The patient was discharged on the thirteenth post-partum day.

Dorland[1] divides cases of watery accumulations in the peritoneal cavity into six types, including serum in fetal peritoneal cavity (true fetal ascites), urine distending urinary tract of fetus (fetal urinary retention), fluid throughout the tissue of fetus (general anasarca of fetus), cystic degeneration of renal structure (congenital polycystic kidneys), cystic degeneration of fetal liver, and fluid distending genital tract of fetus. In all probability the case reported represents a case of true fetal ascites. Although a diagnosis of abnormality was not made, it was suspected from the rapid growth of the uterus in the last six weeks of pregnancy.

REFERENCE

(1) *Dorland, W. A. Newman:* Am. J. Obst. & Dis. Wom. & Child. 79: 474, 1919.

A NEW FORCEPS POSSESSING A SLIDING LOCK, MODIFIED FENESTRA, WITH IMPROVED HANDLE AND AXIS TRACTION ATTACHMENT

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THE purpose for which the obstetric forceps was originally devised was to extract the fetus by the head without damage to either mother or child. As stated by De Lee, "As soon as the right of either is encroached upon, the instrument ceases to be the forceps of obstetrics and becomes simply an instrument of extraction similar to the craniotomy forceps and not so good." It is evident that an instrument simple in design and as nearly foolproof as possible should be the instrument of choice in the hands of novice or expert. If the functional capacity of the instruments used can be improved and their use made safer additional service is rendered to the patient. I believe the forceps here described embodies such improvements.

This forceps embraces three safety features: (1) the Kjelland type sliding lock, (2) modification of the fenestra by closing it on the pelvic side, and (3) one shank extended down and a part of one handle. This modification of the handle reduces the danger of excessive pressure of the blades on the fetal head and is applicable to all Kjelland type forceps, and such forceps would be definitely improved by incorporating this safer handle. The blades have a conventional pelvic curve and well-shaped cephalic curve.

Occasionally the only possible position in which the forceps blades can be applied is with one blade over the right or left side of the posterior parietal and the other blade over the left or right malar bone. Less often, but by necessity it does happen, that an anteroposterior application is the only application possible, or it is made by mistake. In either of the above applications, when the forceps is locked and traction attempted, the tip of one blade presses into the malar bone or the bridge of the nose, as the case may be. This very unfavorable pressure, which may endanger the life of the fetus, can be avoided by use of the forceps here described,

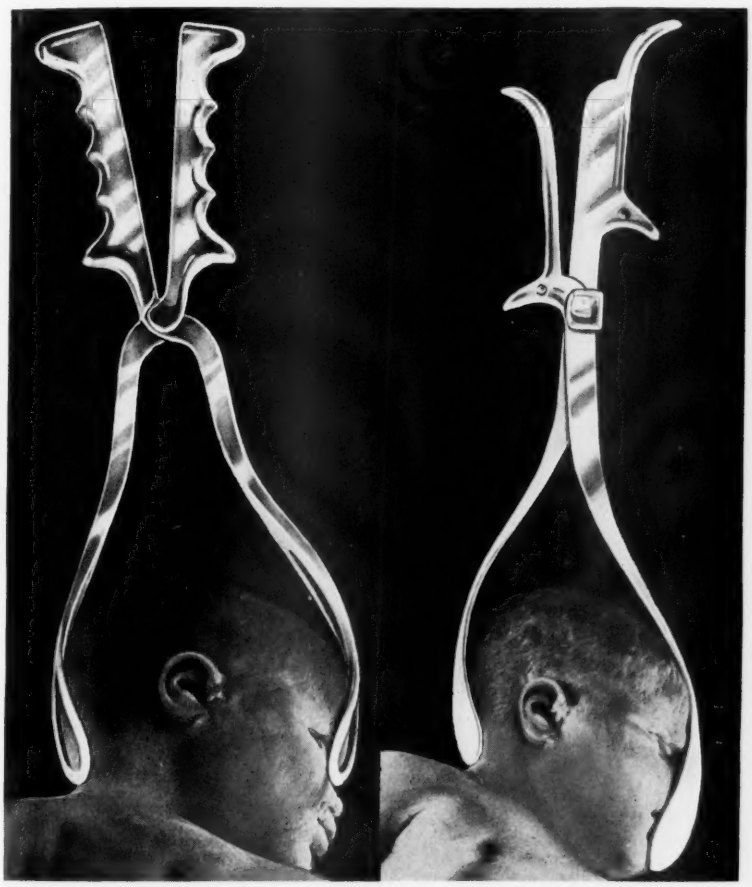

Fig. 1. Fig. 2.

Fig. 1.—Conventional Simpson forceps, revealing a pelvic application to a transverse presentation of the fetal head. Note pressure over nasal bridge.

Fig. 2.—Same application of forceps as shown in Fig. 1. Note advantages of sliding lock when this application is made by necessity or accident. The fit of the forceps is perfect. No spring in shank or blade is needed.

because of its Kjelland type sliding lock. Furthermore, this safety feature reduces the necessity for spring in either the shank or the blades. In fact, the rigidity of the blades decreases the likelihood of the forceps slipping, hence the danger of damage to the fetus is reduced.

The axis traction apparatus is a modification of Dr. A. H. Bill's[1] and McClintock's axis traction attachments. This attachment is simple, is easily applied, and has the direction pointer suggested by Bill. My experience with its use has been extremely satisfactory. It can be used to considerable advantage in the Scanzoni maneuver as described by Bill.

The forceps above described, combined with the axis traction attachment, satisfactorily fulfills every need for traction, at the same time assuring the greatest possible margin of safety. When, however, it is necessary to apply forceps to an aftercoming head the Luikart-Kjelland forceps[2] is preferable because, like the Piper forceps, it has no pelvic curve, and in addition possesses the safety factor of the closed fenestra.

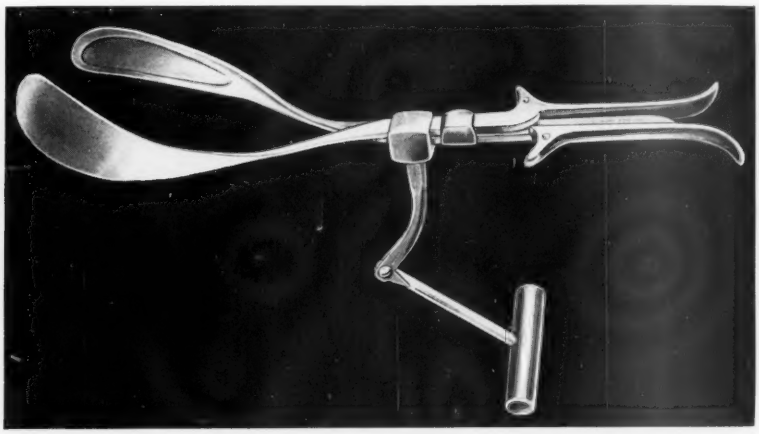

Fig. 3.—Luikart forceps and axis traction attachment. Note standard pelvic and cephalic curves of blades, closed fenestra, sliding lock, modified left handle, axis traction, showing simplicity of attachment and direction pointer.

Hence, these two forceps (the type described in this paper and the Luikart-Kjelland type) and the axis traction attachment should completely fill an obstetrician's needs for forceps, at the same time offering the greatest margin of safety in each operation.

I wish to acknowledge with thanks assistance given by J. Sklar and Company, Long Island City, N. Y., by Dr. Ralph Reese of Chicago and Dr. Maurice E. Grier, of Omaha, for suggestions in regard to the handle modification and by Dr. Frank Murphy of Omaha for assistance in the photography.

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(1) *Bill, A. H.:* Am. J. Obst. Gynec. **9**: 606, 1925. (2) *Luikart, Ralph:* Ibid. **34**: 686, 1937.

Kirchner, W.: Intravenous Narcosis in Obstetrics, Med. Klin. 35: 1342, 1939.

Kirchner emphasizes that the administration of an intravenous narcotic is as much of a hardship on a pregnant woman as any other anesthetic. For a long time he has used the typical morphine-scopolamine twilight sleep to which he has added pernocton and also dilaudid. When evipan was introduced as an intravenous anesthetic he began to make use of it. This drug proved to be helpful for obstetric operations except cesarean section, and version and extraction. Evipan proved useful also in eclampsia regardless of whether the convulsions occurred during pregnancy, labor or after delivery. It is generally believed that evipan has no deleterious effect on the baby although some authors believe the babies are born asphyxiated and remain drowsy for a few days after birth.

Evipan has no effect on uterine contractions during labor. However, since this drug may have a bad effect on the uterus in the third stage, it is recommended that small doses of pituitary extract be given with this drug.

J. P. GREENHILL

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

Greenhill's *Office Gynecology*[1] is a useful book which should prove of value, particularly to the general practitioner and the budding specialist, as it contains many hints and suggestions valuable in office treatment, including such common measures as the vaginal douche, vaginal pessaries, and the treatment of diseases encountered in gynecologic practice. The chapters on gynecologic and obstetric endocrinology, and menstrual irregularities are likewise of real interest. Whether the colposcope should have been included in office gynecology might well be doubted, nor can I agree that intraspinal (subarachnoid) injection of alcohol for pain due to carcinoma of the genitalia, as well as curettage and transabdominal pneumoperitoneum, should be considered office procedures.

—R. T. Frank.

The fifth edition of Young's *Textbook of Gynaecology*[2] has appeared. The first edition was published in 1921. With each edition the text has become more crystallized and is as always, short, clear, sound, and the book is well illustrated. One can see the refinements which successive revisions have made possible. In the present edition, particular attention has been paid to the physiology of the sex organs and the newer understanding of the sex hormones, which are really very well presented, even if some small inaccuracies have crept in. This is a very valuable, short textbook. It may be stated that a few improvements could be made, as, for instance, in the classification of ovarian growths, which is distinctly crude. Tight plugging of the vagina for puberty bleeding, as a routine measure, would not be accepted in the United States.

R. T. Frank.

Martius' *Gynecologic Operations,*[3] which was reviewed in these columns in 1937, has now been translated into English. At that time a very appreciative and laudatory review was given to this valuable contribution to operative gynecology. The illustrations in the original German and in the present American edition are identical, and are noteworthy for their simplicity and striking qualities. No better operative gynecology in short compass is available. The descriptions of operations are clear-cut and sufficiently detailed to be useful, both to the general surgeon and the specialist. While the translation is quite understandable, the English is frequently awkward, even if accurate. In spite of this defect, the book should prove of great value to both student and operator.

—R. T. Frank.

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[1]**Office Gynecology.** By J. P. Greenhill, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, etc., Chicago, Ill. With 106 illustrations, 406 pages. The Year Book Publishers, Inc., Chicago, Ill., 1939.

[2]**Textbook of Gynaecology.** By James Young, Professor of Obstetrics and Gynaecology, University of London, etc. Fifth edition, with 226 illustrations, 425 pages. Adam and Charles Black, Soho Square, London, 1939.

[3]**Gynecologic Operations and Their Topographic-Anatomic Fundamentals.** By Professor Dr. Heinrich Martius, director of Women's Clinic in Goettingen. Authorized English Translation by W. A. Newman Dorland, M.D. With 404 mostly colored illustrations, 486 pages. S. B. Bebour, Publishers. Chicago, 1939.

Obstetrics

This comprehensive presentation of *Obstetrics and Gynecology*[4] in two volumes of approximately one thousand pages each, is offered by some sixty members of the staff of the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-In Hospital under the editorship of Dr. Adair. The unity as well as quality of the two subjects has been recognized, and the text offers a logical consideration of both specialties, as well as their relationships to other branches of medicine. Although the major portion of the work is devoted to obstetrics, the subject of gynecology by no means has been overlooked and the fundamental principles of the abnormalities of the nonpregnant state are thoroughly described. The introductory chapter quickly sums up the modern views of reproduction, the physiology and pathology of the pelvic organs, and presents a general statement of the broad aspects of this branch of medical practice.

The basic biology of the human female continues with general statements on the physiology and anatomy of the generative organs, malignancy and the mechanism of infection and immunity. In a similar manner therapy of various modes in relation to both the reproductive cycle and the nonpregnant organs is offered. The introductory section also deals with nutritional requirements in both normal and abnormal conditions.

The editor's broad vision and a wide knowledge of communal and individual problems is reflected in his very full discussion of maternal care, morbidity, mortality, and the limitations of human reproduction. The life cycle of the human female carries this individual from germ plasma to retrogressive changes of postreproductive life. This section is extended to include such complications as sterility, infertility, and deviations of marital physiology.

Pregnancy and its abnormalities lead from the anatomy, physiology, and hygiene of the nonpregnant to that of the pregnant woman with a discussion of the diagnosis of pregnancy, early termination, abnormal situation, and early and late toxemias of pregnancy. In the latter section on the late toxemias of pregnancy, one finds an extensive presentation of the subject, a wide review of the literature and a recapitulation of the extensive clinical and laboratory research on the toxemias of pregnancy which has emanated from the Lying-In Hospital of Chicago during the past decade. In discussing the parturient woman, a similar logical sequence is used. The mechanism and management of normal labor is followed by a discussion of the third stage. Realizing that the major portion of obstetrics in the United States is not carried out in the narrow confines of the hospital delivery room, the editor has offered a short, but, thoroughly developed plan and technique for home delivery. Concise directions and suggestions for the treatment under emergency circumstances of the various complications of labor, hemorrhage, shock, toxemia, and abnormal situations in regard to the newborn infant are given.

The text continues with the pathology of labor, management of breech and other abnormal attitudes. Such evidence of pathologic labor, as premature labor, prolonged labor, and the cord dystocias are discussed fully and followed by the fetal phases, the abnormalities of which lead to antenatal and intrapartum death. In discussing placenta previa, the need for smooth organization of the hospital in handling hemorrhage is stressed. The value of the transfusion, the success of blood banks, and the various methods of vaginal approach to placenta previa are described. In spite of its possible attendant hemorrhage the lower segment operation is favored for abdominal delivery in placenta previa.

As the treatise continues in the second volume, the problems of the puerperium and the newborn infant are discussed. The problems of pelvic regeneration and repair are followed by the nursing care of the puerperal woman. Puerperal infection is regarded as a contact wound infection, and those with hemolytic streptococcus as practically always exogenous. The therapeutic effect of sulfanilamide in such

[4]**Obstetrics and Gynecology.** By the Departmental Staff of the University of Chicago and Other Contributors. Edited by Fred L. Adair, Mary Campau Ryerson Professor and Chairman of the Department of Obstetrics and Gynecology, in the University of Chicago, etc. Volume I, 1000 pages with 359 engravings and 14 plates. Volume II, 1031 pages with 304 engravings and 10 plates. Lea & Febiger, Philadelphia, 1940.

conditions is cautiously evaluated. Obstetric facts in end results, child growth and development are succinctly stated. Stress is laid on the care of the premature. The diseases of the newborn are discussed not only from a medical and surgical standpoint, including congenital deformities and orthopedic lesions, but also such conditions as asphyxia and birth trauma.

Taking up in an extended manner the gynecologic conditions previously referred to in various places of the text, the neoplastic diseases are first considered.

The incidence of cervical stump carcinoma following subtotal hysterectomy for myoma is regarded as counterbalancing the higher mortality of the total operation. Here the intrauterine application of radium is considered preferable to the use of x-ray in nonoperative treatment. The discussion of uterine carcinoma is extensive, various methods of classification and grading are included. The more recently differentiated ovarian tumors are fully described. The choice and nature of the operation to be performed in endometriosis is well analyzed. In discussing cystic degeneration of the chorionic villi and the malignant process which may follow, the text suggests that in view of the radiosensitivity of chorionepithelioma, irradiation should be carried out in conjunction with operation. Gynecologic displacements and relaxations are dealt with particularly in regard to obstetric prophylaxis of the lesions. It is concluded that no single method of operative therapy is adapted to all forms of genital prolapse. In a similar manner the end results of obstetric infections on the pelvic tissues is described.

Gonorrhea is considered from both its obstetric and gynecologic aspects, its relationship to fertility as well as to pregnancy. In discussing the treatment of gonorrhea by sulfanilamide, the text suggests that the fetus may be more susceptible to this drug than the mother. Although syphilis is discussed mainly from the standpoint of its relationship to reproduction, no suggestions as to treatment occur here, and it is only later in the section on internal medicine that one picks up the therapy of syphilis during pregnancy.

Tuberculosis is considered both from the standpoint of its genital lesions and by a consideration of the treatment of the woman with pulmonary tuberculosis who becomes pregnant. Early abortion is recommended for active tuberculosis, but otherwise general lines of treatment with only indicated obstetric surgery are suggested.

The most recent plan of treatment of trichomonas infestation in the Chicago Lying-In Hospital consists in the use of lactose intravaginally to replace the depleted carbohydrate state of the vaginal mucosa and thus effect a return of the normal vaginal flora and acidity. In a discussion of chronic cervicitis, judgment has been reserved on conization and electrocoagulation because of tissue destruction and scarring.

The third section in this volume consists of a discussion of the relationship of various medical and surgical diseases to reproduction in its various phases as well as to function of the pelvic organs. This section also includes an ample presentation of roentgenologic diagnosis in obstetrics especially with reference to pelvimetry and fetometry.

The final section discusses pre- and postoperative management of obstetric and gynecologic procedures according to the schedule used in this Chicago clinic. It is followed by an excellent chapter on the subject of intravenous therapy and blood transfusions, with a discussion of the banking of blood and its derivatives. Anesthetic agents and methods are discussed. In this section, the authors have included a consideration of the various methods of amnesia-analgesia during labor. This particular chapter is marked by an unusual degree of detail in treating the subject.

There is a very concise presentation of cesarean section with excellent illustrations of the lower segment operation. There is an excellent recapitulation of morbidity and mortality of cesarean section. The chapter on hysterectomy is followed by a presentation of version and forceps deliveries, and a short discussion of the destructive operations.

An appendix giving various types of diets which might be used in the obstetric-gynecologic services with details as to menus and food values is a valuable addition. The techniques of many clinical laboratory tests used in routine work in the Chicago

Lying-In Hospital are appended and the book is completed with a brief discussion of the relationship of vital statistics to obstetric and gynecologic practice, with some definitions and a presentation of the coding of puerperal deaths agreed upon for the present decade at a recent meeting of the International Commission on Causes of Death.

The two volumes represent a thoughtful consideration and excellently balanced presentation of the principles of the two specialties. The logical development of the text with an avoidance of duplication and the extended consideration of the broad aspects and interrelationships with the basic sciences and other clinical entities makes these two volumes a reference work of unusual merit and value which may be highly recommended.

—*Philip F. Williams.*

The title of this volume, *The Management of Obstetric Difficulties*[5] does not indicate its scope; it is actually a complete textbook of obstetrics for practitioners. It differs from a textbook for medical students as a clinical paper differs from a medical editorial. The discussions come directly to the point, historical background is mentioned but minimized, little space is given to facts of academic interest only, discussions of therapy are followed by a detailed tabulation of recommendations. The author does not say, "Sedation is indicated," he specifies what, and how much, and how it is to be given. His entire book is pleasantly free of vagueness. The preface states, "I favor the expression of my own preferences in undecided issues" and this policy has been skillfully carried out. The author's personal views are clearly, but unobtrusively, presented as his own. In general substance the work is sound; to follow its precepts would be to practice safe obstetrics.

Adverse criticism of so good a work seems a little unkind. Yet it is true of this book, as of many others in medicine, that the services of a professional grammarian would add polish and reduce verbiage. Occasionally an explanation is overworked. For example, pelvic hyperemia in pregnancy is given as a cause for deposition of fat on the hips, for symphysial separation, and for increased susceptibility to trichomonas infection.

The volume is recommended to general practitioners, graduate students, and men preparing for the American Board examination. Even the experienced obstetrician will find it worth reading. Especially useful are the references to recent and important literature.

—*Pendleton Tompkins.*

The conception of this joint volume, *Obstetrics and Gynaecology*,[6] was based on the feeling of the original editorial board that these two subjects should be combined in teaching as well as in practice, and an excellent chapter is devoted to the nature of the correlation. Some changes in the authorship have been occasioned by death, and in the present editorial board, headed by Kerr, faculties of obstetrics and gynecology of Glasgow, Aberdeen and Edinburgh are represented.

The book retains the form and subject content of the two previous editions. In the revisions there has been incorporated new material with regard to the physiology of the reproductive organs and an excellent treatise on nutrition, full consideration of chemotherapy of infections, a discussion of the more recently described ovarian tumors. The section on radiology and roentgen technique in obstetrics and gynecology, re-written by a new contributor, includes references to much of the recent literature.

As expressed in the previous reviews of this volume, it must be considered an excellent combined textbook of the two subjects, not only for the student but for

[5]**Management of Obstetric Difficulties.** By Paul Titus, Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh, etc. Second edition, 868 pages, with 368 illustrations and 5 color plates. The C. V. Mosby Company, St. Louis, 1940.

[6]**Combined Textbook of Obstetrics and Gynecology.** Revised and rewritten by J. M. Munro Kerr, R. W. Johnstone, James Hendry, Dugald Baird, James Young, Donald McIntyre, E. Chalmers Fahmy, with additional contributions by Charles McNeil and G. Jackson Wilson. Third edition, 1192 pages with 499 illustrations and numerous x-ray plates. Williams and Wilkins Company, Baltimore, 1939.

the general practitioner as well. If any criticism could be offered it would be that the discussion of gynecologic operations was exceedingly brief. This, however, is explained in the attitude of the authors that surgical technique in the treatment of women cannot be based on book reading but requires a long clinical apprenticeship.

—Philip F. Williams.

Exhaustion of the first edition within a relatively short time offered Beck the opportunity to thoroughly revise his excellent *Obstetrical Practice*,[7] particularly by the addition of much new material, e.g., a new chapter on retained and adherent placenta. There are two features which clearly distinguish this volume from similar texts, namely the large number of instructive, mostly diagrammatic illustrations, and the inclusion of an unusual amount of detail information, such as average percentage saturation with oxygen of blood coming from the uterus; maternal placental blood pressure; differences in blood constitution of mother and fetus; nitrogen and calcium storage, etc. The discussion of adequate food supply during pregnancy includes two and one-half pages of tables giving protein, carbohydrate, fat, calcium, iron and vitamin contents and caloric values of all the usual food stuffs. A wealth of details can be found in the two chapters devoted to contracted pelves.

The index is inadequate. No reference can be found in it to undue prolongation of pregnancy, the overcarried infant, induction of labor, episiotomy, birth injuries, etc. Obviously this is but a minor shortcoming which could be easily corrected in a subsequent edition.

—Hugo Ehrenfest.

In view of the widespread and increasing interest in the preservation of fetal and neonatal life, this book *Fetal and Neonatal Death*[8] by Potter and Adair is timely. Those who are interested in attempting to salvage what is possible of the potential population loss will find much to aid them in their efforts.

The subject matter is divided into five chapters: The first chapter presents a statistical résumé of the present loss of life by stillbirths and neonatal deaths, followed by the physical characteristics of the normal fetus and infant. The technique of the fact finding by post-mortem examination is quite detailed. It is to be hoped that many hospital pathologists may note this section. There is an excellent discussion of anoxemia as a cause of death. Under special pathology, the specific lesions of the various organs and systems are discussed in relation to the manner in which they may cause fetal and neonatal deaths.

It is to be hoped that this book may become a working manual in every maternity hospital and that the general hospital pathologist may inform himself from it as to the exacting technique necessary in determining at autopsy the cause of death in the fetal or neonatal period.

—Philip F. Williams.

Leon's *Radiology in Obstetrics*[9] was a presentation officially designated as the subject in 1939 before the Buenos Aires Obstetric and Gynecologic Society. It is a pamphlet of but eighty-seven pages, faultlessly gotten up, with excellent reproductions of x-ray plates. The subjects cover practically every phase briefly but clearly. The use of x-ray for the pregnant mother in order to determine the kidney and intestinal conditions, fetal conditions from the fourth month, determination of presentation, multiple pregnancy, monsters, intrauterine death and extrauterine pregnancy are all discussed. The amount of information contained in such short compass is amazing.

—R. T. Frank.

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[7] **Obstetrical Practice.** By Alfred C. Beck, Professor of Obstetrics and Gynecology, Long Island College of Medicine, Brooklyn, etc. Second edition, 858 pages, 1043 illustrations. Williams & Wilkins Company, Baltimore, 1939.

[8] **Fetal and Neonatal Death.** By Edith L. Potter, M.D., and Fred L. Adair, M.D. University of Chicago Press, Chicago, Ill.

[9] **La Radiologia en Obstetricia.** Estado Actual de sus Aplicaciones Practicas. By Juan Leon, Professor Adjunto de Clinica Obstetrica de la Facultad de Ciencias Medicas de Buenos Aires. Editor "El Ateneo," Buenos Aires.

In *Obstetrical Manikin Practice*,[10] Dr. McNeile has developed teaching material for six seminars. This demonstration course is offered to supplement clinical material and to offer the student an opportunity to try out various procedures which he may have seen performed in clinic. In addition to various obstetric operations through the vaginal route there has been included a demonstration of the mechanism of labor in abnormal pelves which may do much toward assisting a student in an understanding of the physics of parturition.

—*Philip F. Williams.*

Dr. Marshall in this monograph *Caesarean Section, Lower Segment Operation*,[11] strongly emphasizes the advantages of this procedure. He has performed some 250 such operations, and may be regarded as well qualified to discuss its advantages, technique, and dangers.

Opening with an interesting and carefully documented history of the early suggestions and later attempts at the operation, he discusses the improvements in bacteriologic and surgical technique which made possible the procedure of today. He discusses the types of anesthesia available, and concludes that local anesthesia should be much more widely employed; that ether should be reserved for cases of great urgency, while spinal should be used in a few cases in whom considerable technical troubles can be foreseen. The physiology of the development of the lower uterine segment and the nature of the incision and technique of this type of operation, well illustrated, is comprehensively discussed. In view of the fact that this operation is often undertaken in the presence of infection in a pregnant woman, the author has stressed the various protective procedures against infection such as vaginal antisepsis, care of the field of operation, method of peritonization of the incision and drainage of the uterus and peritoneal cavity and of the abdominal incision.

In consideration of Doerfler's operation he withholds judgment on the suggested eventration of the uterus. The treatment of hemorrhage and the use of oxytocics are considered, and there is a discussion of the use of this type of operation for placenta previa. He does not ascribe any superiority to the lower segment operation over the classical one in the treatment of placenta previa unless there is a concomitant infection. The various potentialities for evil results of the operation are mentioned as are suggestions as to how to obviate them.

In closing the monograph he states that there was an unreduced maternal mortality of 0.0 per cent, unreduced fetal mortality of 5.7 per cent, and total morbidity rate of 23.5 per cent in his series. In 246 operations, 70 were performed for suspect of present infection, 43 for placenta previa, 19 for toxemia, 14 for heart disease. The results are surprisingly favorable in view of such a large proportion of poor operative risks. A splendid consideration of an operation with a constantly widening use.

—*Philip F. Williams.*

Normal Obstetrics[12] by Raul Briquet is a well-organized and documented general obstetrics. Particular emphasis has been placed on the physiology and pathology of conditions. The book is fully up to date. The author has incorporated and utilized the best from European and American literature. The 423 illustrations are excellent, the majority from classic and well-known sources, to whom due credit has been given.

—*R. T. Frank.*

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[10]**Obstetrical Manikin Practice.** By Lyle G. McNeile, Professor of Obstetrics and Gynecology, University of Southern California School of Medicine, etc. With 38 illustrations, 111 pages. Williams and Wilkins Company, Baltimore, 1939.

[11]**Caesarean Section, Lower Segment Operation.** By C. McIntosh Marshall, Honorary Assistant Surgeon, Liverpool Maternity Hospital, etc. With 2 plates and 107 illustrations, 230 pages. Williams and Wilkins Company, Baltimore, 1939.

[12]**Obstetricia Normal.** Professor Raul Briquet, lente catedrático de Clinica Obstétrica e Puericultura Neonatal da Universidade de S. Paulo. Com 427 figuras das quais 37 em duas e mais cores. Livraria Editora Freitas Bastos, Rio de Janeiro, 1939.

This small monograph on *The Estimation of Pelvic Capacity*[13] by Dr. Thoms recapitulates the methods which may be employed in ascertaining the capacity of the pelvis in the living subject, and discusses the findings resulting from such investigation. Roentgenometric technique is presented in detail and the clinical application of the findings is fully discussed. While much of the material in this recapitulation of the problem has already appeared, the monograph should be extremely useful to all obstetricians.

—Philip F. Williams.

Into this small volume, *Synopsis of Obstetrics*,[14] Litzenberg, by omitting all theoretic and controversial data, has packed a great deal of useful knowledge. The text marked by clarity and brevity describes the normal reproductive cycle, then the abnormal conditions of the pelvis, passenger, and mother. While the discussion of operative obstetrics is short, it is definite as to indication and technique. The complications of the puerperium are discussed, including both immediate injuries and late sequelae.

Such a book should be of use to the student in review and as a pocket manual for the practitioner. Possibly an additional chapter or two on the premature child and the early complications of neonatal life might have been added.

—Philip F. Williams.

In the second edition of his *Die Geburtshilflichen Operationen*[15] Martius has presented a beautiful atlas of operative obstetrics. The 281 illustrations explain pictorially practically all types of operations used in connection with operative deliveries. The text is short and each small paragraph emphasizes some point in the technique pictured. The physics of normal and abnormal labors are explained in the opening chapters. A note of marked value is found in the discussion of the operations which may be practiced in the home and those for which hospital surroundings are necessary.

—Philip F. Williams.

Congenital Malformations,[16] by Douglas P. Murphy, a study of parental characteristics, with special reference to the reproductive process, is a short monograph, the data for which were obtained by a scrutiny of the birth and death records of Philadelphia, and a house-to-house investigation of the malformed individuals. It is a basic study which, though it does not elucidate the actual causes of malformation, contains important facts.

Malformations are more common among siblings and are prone to be identical in a family. Mating has been classified as efficient and inefficient, and is divided into various degrees. In Philadelphia, 1 in 213 live births showed malformations, and 25 per cent of malformed newborn were stillbirths. The rate among whites was twice as great as among negroes. Twenty-five per cent more malformations occurred in families in which a previous malformation had occurred. It appears that older mothers were more likely to give birth to malformed individuals, and this likewise applied to children born late in a family. Polyhydramnios and abnormal fetal movements had been noted in many cases. If two or more malformations occurred in the same family, 50 per cent were found identical. Of the malformed infants, 90 per cent were either stillborn or died within the first year. The influences producing malformations definitely were those in the germic cell

[13]**The Estimation of Pelvic Capacity.** By Herbert Thoms, M.D. Associate Professor of Obstetrics and Gynecology, School of Medicine, Yale University. The American Journal of Surgery, New York, 1940.

[14]**Synopsis of Obstetrics.** By Jennings C. Litzenberg, M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis, Minn. 157 illustrations, 5 in color, 376 pages. The C. V. Mosby Company, St. Louis, Mo., 1940.

[15]**Die Geburtschilflichen Operationen.** Ihre Ausführung und Anwendung. Von Prof. Dr. Med. Heinrich Martius. Zweite, verbesserte Auflage, mit 281, zum Teil farbigen Abbildungen. Georg Thieme, Leipzig, 1940.

[16]**Congenital Malformations.** By Douglas P. Murphy, Assistant Professor of Obstetrics and Research Associate in Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania. University of Pennsylvania Press, Philadelphia, 1940.

prior to fertilization. The diet of many mothers who gave birth to malformed children was found defective in calcium, phosphorus, iron, and vitamins. This is an important contribution.

—*R. T. Frank.*

Laforet's monograph on the *Early Diagnosis of Pregnancy*[17] takes up the historical aspects and the clinical signs. The main portion, however, is devoted to the biologic tests for pregnancy, particularly the Aschheim-Zondek test.

The monograph contains a large bibliography, a good synopsis of the situation, but no new contribution of any kind.

—*R. T. Frank.*

This monograph[18] deals with the statistics on Italian mothers who have borne at least seven live children. It was found that the onset of their menarche was normal, that the climax occurred late, and hence their period of sex activity was prolonged. Various other observations dealing with the subject are contained in the many tables of this monograph which is based on the population of all portions of Italy.

—*R. T. Frank.*

In his monograph, *Grundlagen der Schwangerenernaehrung*[19] Gaehtgens discusses the significance of present world-wide studies on nutrition. Regarding pregnancy as a nutritional problem, he brings out reasons for the exact determination of caloric intake in various energy-producing and protective foods. The metabolism of reproduction and the development of the fetus afford an opportunity to bring out the necessity for careful selection of the various food elements, whose chemical and physical qualities are described at length. Under the vitamins he discusses not only the outstanding deficiencies but also relative conditions which lead to the subclinical deficiency states. He describes laboratory tests for the determination of vitamin deficiencies.

There is an excellent chapter on the relationship of nutrition and lactation. The practical aspect of the subject is stated clearly with a consideration of how the pregnant woman can be educated to the need for the properly assorted diet, and how she can purchase it on a limited income. Gaehtgens feels that a good supportive diet can be purchased for 30 R.M. per month, which at the present rate of exchange will be $12 in American money. According to a recent local government publication this sum would allow a wide range of values in an American family. Gaehtgens has appended a very complete bibliography, a number of appendices summarizing vitamins, their artificial substitutes, food values. A week's diet for a pregnant woman is detailed as to values and protective substances. The monograph is an excellent presentation of a much neglected subject.

—*Philip F. Williams.*

Pictorial Midwifery[20] by Sir Comyns Berkeley carries the sub-title *An Atlas of Midwifery for Pupil Midwives.* Though specifically designed "for pupil midwives preparing for the state examination," this small volume might prove, in the reviewer's estimation, also of considerable practical value to the medical student. While containing but few illustrations which could not be found in every standard textbook of obstetrics, this atlas is characterized by detailed description of each illustration in the appended legend. These legends represent the entire text matter and cover all important features in the anatomy, physiology and pathology of pregnancy, labor, and the puerperium. The drawings are well done and in each instance clearly present the particular points to be shown.

—*Hugo Ehrenfest.*

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[17]**El Diagnostico Precoz Del Embarazo.** Par Dr. Carlos Colmeiro Laforet. 244 pages, illustrated. Libreria "Gali," Santiago de Compostela, 1940.

[18]**Il Ciclo Sessuale delle Madri delle Famiglie Numerose.** A cura di Corrado Gini e Pia de Orchi. Comitato Italiano per lo studio dei Problemi della Popolazione, Roma, 1939.

[19]**Grundlagen der Schwangerschaften-Ernaehrung.** Von Dr. Med. G. Gaehtgens. Universitaets Frauenklinik zu Leipzig. 142 seiten mit 9 abbildungen. Verlag von Theodor Steinkopff, Dresden, 1940.

[20]**Pictorial Midwifery.** By Sir Comyns Berkeley, Chairman of the Central Midwives Board, Consulting Obstetric and Gynecological Surgeon to the Middlesex Hospital, etc. Third edition, 166 pages. Williams & Wilkins Company, Baltimore, 1939.

As childbearing is a natural process, pregnancy should be a healthy, happy time. Thus states the author in his preface in *Expectant Motherhood*[21] and proceeds to show in subsequent pages how this may be achieved. He answers well the "whys" and the "wherefores" which intelligent women are desirous of being informed about, and this is done in an effort to supplement rather than confuse the doctor's instructions. The contents of the book very completely and satisfactorily cover the accepted facts of the prenatal period, of labor, and of the puerperium, although one may question the value of the somewhat technical descriptions in the chapter on growth and development. Chromosomes and trophoblast are still outside the domain of appreciation by the laity. The comparative descriptions of various "painless labor" procedures may lead to a personal selection of method and consequent dictation to the doctor. However, the book as a whole is a very serviceable addition to the many books on the subject which are finding deserved circulation among the intelligent laity. It will undoubtedly explain many things which should be known to our prospective mothers.

—*George W. Kosmak.*

Miscellaneous

It is an esthetic pleasure to study the *Atlas of Surgical Operations*[22] by Cutler and Zollinger, which is beautifully illustrated by Mildred B. Codding. The authors present this as "a book about surgical craft." It is designed to supply the intimate technical steps of surgical operations; ". . . . to bring forward to the unfledged surgeon in a single small volume the simpler and standardized procedure of modern surgical practice." These aims have been excellently attained.

After a very short introduction, the atlas is arranged so that on one page appears the text, which is extremely short but adequate; upon the other page, the illustrations of the operative procedure in various steps.

The entire subject of general abdominal surgery is covered, and in addition, gynecologic operations, including vaginal plastics, infections of the hands, sutures of the nerves and tendons, the treatment of varicose veins, periarterial sympathectomy, and amputations are shown in eighty-four plates.

The illustrations deserve special commendation. They are line drawings, exceptionally clear, delicate and true to nature without exaggeration, every step being clearly indicated. I welcome this departure from the current half-tone which so readily covers many sins of inaccuracy and of poor drawing.

The authors have shown excellent judgment in their selection of material and types of operation. It would of course be possible to differ here and there with the value of the techniques employed but on the whole, no more comprehensive and readily understandable book on surgical technique has appeared in many years. This book should enjoy a wide popularity.

—*R. T. Frank.*

Specialties in Medical Practice[23] under the editorship of Edgar van Nuys-Allen appears in loose-leaf form in two volumes, by numerous authors. This work is intended to be a ready source of information to all who practice medicine, and is meant particularly for the specialist who may desire to inform himself about other specialties. It is likewise meant for the medical student.

Volume I contains seven chapters covering ophthalmology; diseases of the ear, nose, and throat; neurology; psychiatry; the vitamins and vitamin deficiency diseases; allergy; and orthopedic surgery.

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[21]**Expectant Motherhood.** By Nicholson J. Eastman, M.D., Professor of Obstetrics in Johns Hopkins University and Obstetrician-in-Chief to the Johns Hopkins Hospital. Little, Brown & Co., Boston, 1940.

[22]**Atlas of Surgical Operations.** By Elliott C. Cutler, Moseley Professor of Surgery, Harvard University, etc., and Robert Zollinger, Assistant Professor of Surgery, Harvard University, etc. Illustrated by Mildred B. Codding, 179 pages. The Macmillan Company, New York, 1939.

[23]**Specialties in Medical Practice.** Edited by Edgar van Nuys-Allen, Chief of a Section in the Division of Medicine, The Mayo Clinic, Rochester, Minn., etc., with a Foreword by Donald C. Balfour, Consultant in Surgery, the Mayo Clinic. Loose-Leaf, in two volumes, illustrated. Thomas Nelson and Sons, New York, 1940.

In the second volume are taken up obstetrics and gynecology; endocrinology; urology; proctology. Dermatology and syphilology are in preparation. The endocrine aspects of the ovary are not included under endocrinology, as they have been dealt with to some extent under obstetrics and gynecology.

This publication has the advantage of its loose-leaf format with the possibility of keeping it constantly up to date.

—*R. T. Frank.*

The Bodanskys, Meyer and Oscar, have produced a general treatise of medicine, *Biochemistry of Disease*,[24] viewed from the angle of biochemistry. Within its 684 pages, the relation of biochemistry to the understanding of the pathogenesis, the course and the treatment of disease is shown in a clear, sequential and understandable fashion. This very difficult achievement has been accomplished by leaving out many elementary discussions and details of laboratory technique, and by arranging the material according to clinical entities. Nevertheless, innumerable of the current and constantly used procedures are given in sufficient detail to be readily followed by the clinician.

The subjects have been covered in 18 chapters which include diseases of blood, heart, respiratory, kidney and urinary tracts; the digestive tracts, the liver and biliary systems also are dealt with. The chapter on endocrinology includes pancreas, adrenals, pituitary, thyroid parathyroid, and male and female gonads. The diseases of bone, muscle, disorders of nutrition and of metabolism are taken up. The final chapter includes neurologic and psychiatric disorders.

It is surprising how this immense amount of material has been incorporated in one volume in such a clear-cut and readily understandable fashion. The bibliographies at the end of the chapters also make the book of value for reference.

Any physician or surgeon who is interested in following the steady advances of biochemistry, will find this book of utmost importance to him, either for referring to individual facts or by gradual rereading the individual chapters to clarify his knowledge, and to enable him to understand what biochemical laboratory tests really signify.

—*R. T. Frank.*

Biological Symposia,[25] edited by Jaques Cattell, was conceived to celebrate the one hundredth anniversary of the cell theory attributed[2] to Schleiden and Schwann. The monograph covers the cell theory, mating types, and their mating action in the ciliate infusoria and their chromosome structure, written by numerous well-known workers in this field. These articles plainly show that Schleiden and Schwann have received too much credit, as many predecessors whose work dates back for more than two hundred years had laid the foundation stones upon which the cell theory was actually based. Moreover, the intervening century has demonstrated that, as originally conceived, this theory requires many modifications. Nevertheless, the popularization of the cell concept must be credited with having speeded up the work immeasurably. The articles make most interesting reading both for the profession and for the laity.

—*R. T. Frank.*

The eighth edition of Jordan's *Textbook of Histology*[26] has appeared. This standard textbook has slowly developed and crystallized since it first was published in 1916. In the present edition, the chapters on muscle, endocrine organs, the female reproductive system, and the blood vascular system have undergone particularly thorough revision. The author has wisely dropped the chapter on histologic technique and directions for laboratory work.

This is an adequate textbook, very well illustrated, with illustrations drawn from standard sources, and some of the illustrations in colors. Another improvement is

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[24]**Biochemistry of Disease.** By Meyer Bodansky, M.D., and Oscar Bodansky, M.D. 684 pages. The Macmillan Company, New York, 1940.

[25]**Biological Symposia.** Edited by Jaques Cattell, Editor of The American Naturalist and American Men of Science. 238 pages, illustrated. The Jaques Cattell Press, Lancaster, Pa., 1940.

[26]**A Textbook of Histology.** By Harvey Ernest Jordan, Professor of Anatomy and Director of Anatomical Laboratories, University of Virginia. Eighth edition, 690 pages, 609 illustrations. D. Appleton-Century Co., Inc., New York, 1940.

a bibliography which concludes the volume, because this book is not only used by medical students, but is of utmost value to physicians in looking up the fundamental morphology. The concept of the endocrine glands is somewhat loosely drawn as many will still take exception to including the carotid and coccygeal glands among the endocrine organs, and would prefer to have the pancreas as well as the male and female gonads more closely associated with the endocrines. Each edition has seen improvement in this work which is always kept fully up to date.

—*R. T. Frank.*

The first Chilean Surgical Congress[27] was held in 1939. Its proceedings are contained in a large, handsome volume of 565 pages. The three themes officially assigned were acute pancreatitis, treatment of uterine fibroids (surgical, radiotherapeutic, as well as experimental, the latter based on the fundamental observations of Nelson made in 1937), and fractures of the neck of the femur. In addition, a series of articles covering various surgical and gynecologic-obstetric subjects were reported. The participants in this activity were mainly from Chile and Argentina although other South American states were represented. The articles are profusely and well illustrated.

—*R. T. Frank.*

In this sixth edition of *The Art of Anesthesia*,[28] Dr. Flagg has inserted a great deal of new material. A prominent suggestion contained in the present volume is in regard to those who are skilled in anesthesia becoming the leaders in the movement to provide promptly available services to meet the existing asphyxial mortality of the 1,000 deaths a week in the United States, and that such an organization be the leaders in directing resuscitation teams.

There is a critical review of the latest views relating to the agents commonly employed as basal anesthetics. This section should be of interest in the consideration of the various methods of relieving pain in labor which are commonly employed.

Flagg states in regard to chloroform that it should cease to be used as an anesthetic in obstetrics and regards gas-oxygen as valuable only as an analgesic in obstetrics. He says that full-term babies in utero are more susceptible to ethylene gas than their mothers; therefore, the gas is not safe for operative obstetrics.

There is an excellent chapter on the postoperative nursing of the patient who has had various types of inhalation anesthesia. For the benefit of students, as well as anesthetists, he has provided a new chapter on preanesthetic physical examinations.

Obstetric anesthesia forms the subject of a well-thought-out section. In connection with the suggestion that anesthetists direct resuscitation efforts, the chapter on artificial respiration has been entirely rewritten. In the chapter on the causes of deaths in anesthesia, Flagg presents a very concise discussion of asphyxia of the newborn and its treatment. The subject matter is comprehensive and the book should be in the armamentarium of all anesthesia departments.

—*Philip F. Williams.*

The National Organization for Public Health Nursing offers for the third time, a *Manual of Public Health Nursing*[29] to suggest procedure, which may serve as a guide to the public health nurse in the field. This may be applied to the small community, county, large city services or state. As the scope of public health nursing in recent years has increased under governmental and allied agencies, the need for an up-to-date manual is apparent.

In the first part of the book, administration and organizations are thoroughly discussed in reference to the relationship of public health nursing to other services, the nurse's work and education. The education of the family as to health is thoroughly detailed.

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[27]**Primer Congreso Chileno y Americano de Cirurgia.** Imprenta Universitaria. Santiago de Chile, 1939.

[28]**The Art of Anesthesia.** By Paluel J. Flagg, M.D., Visiting Anaesthetist to Manhattan Eye and Ear Hospital, etc., New York. Sixth edition, revised. With 161 illustrations, 491 pages. J. B. Lippincott Co., Philadelphia, 1939.

[29]**Manual of Public Health Nursing.** Prepared by the National Organization for Public Health Nursing. Third edition, 529 pages. The Macmillan Company, New York, 1939.

More specific and detailed services which the nurse may be called upon to carry out are given in Part III. The section on maternity services is a complete manual on obstetric nursing whether it be in rural areas or congested city districts. The directions are clearly and concisely given. The nurse is expressly directed as to her duties in regard to the physicians and hospital services. The technique recommended is above reproach. A new and pertinent section deals with recent public health work in the control of venereal diseases.

This is an excellent book. The directions are concise, material is wisely written, and the book is warmly recommended not only to public health nurses but to those who direct the activities of such women.

—Philip F. Williams.

This volume on *Sexual Pathology*[30] by the late Magnus Hirschfeld has been condensed from the original three-volume edition. In it Hirschfeld has divided the subject matter into three main divisions: sexual symbolism, hypereroticism, and impotence.

In the section devoted to Sexual Symbolism he details the nature of the various abnormal attractions, both masculine and feminine. Under Hypereroticism he discusses the quantitative variations of the sexual urge and its various types of output, including murder. Under the section on Impotence there is a general discussion of potency and fertility with case histories relating to the various types of impotence and frigidity in both male and female. Hirschfeld offers few, if any, suggestions as to the therapeusis of these abnormal ideas, practices, or conditions, which is to be regretted, since the treatment of these aberrations of the sexual instinct is difficult.

—Philip F. Williams.

This volume on *Sex in Marriage*[31] by Groves and Groves is a clear and common sense presentation of many of the problems which affect marriage. The long clinical experience of the authors, dealing in family problems, has eminently fitted them to write this book. The problems of sexual adjustments are described with an understanding philosophy which should make the book valuable to many individuals. A very practical chapter on birth control answers many questions often asked by anxious couples. To those whose practice includes discussion of family problems, particularly regarding marriage, this book may be highly recommended.

—Philip F. Williams.

Sex in Life[32] by Eugen Steinach is a translation from the German. It is really a popular scientific account of all of Steinach's researches which he was motivated to write in order to clarify misunderstandings and misstatements. It is likewise an autobiography of this now seventy-nine-year-old scientist. The book is interestingly written, and in the main, focuses upon Steinach's own contributions, although some credit is given to others.

The translation is excellent. The experiments based upon physical and psychical investigations to determine the causes of erotization are described in detail. Transplantation experiments, first of the testicle (begun in 1884) and later of the ovary, with re-establishment of sexual potence, as well as the well-known femininization and masculinization experiments, are recounted. The less well-authenticated transplantation on the human are described by the author, as well as rejuvenation by vasoligation and the production of experimental hermaphroditism. Finally sex hormone therapy is referred to. This book is very personal, very well written, somewhat boastful, but informative.

—R. T. Frank.

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[30]**Sexual Pathology.** By Magnus Hirschfeld, M.D. Authorized Translation by Jerome Gibbs. Originally published in three volumes. 368 pages. Emerson Books, Inc., New York, 1940.

[31]**Sex in Marriage.** By Ernest R. Groves, Professor of Sociology, University of North Carolina and Gladys H. Groves, Director of the Marriage and Family Council, Inc., Chapel Hill, North Carolina. Emerson Books, Inc., New York, 1940.

[32]**Sex and Life.** Forty Years of Biological and Medical Experiments. By Eugen Steinach, M.D., Ph.D., formerly Professor of Physiology at the University of Vienna. The scientific values adapted to the lay reader by Josef Loebel, M.D. 252 pages. The Viking Press, New York, 1940.

Kehrer's monograph on the *Psychical Diseases of the Menopause*,[33] from its clinical aspects, discusses the many mental changes which can be found at this stage of life, particularly menopausal melancholia and senile dementia. The monograph is difficult to read because of lack of adequate arrangement.

—*R. T. Frank.*

The useful and widely appreciated *Medical Dictionary*[34] by Stedman has appeared in a new (fourteenth) and extensively revised edition. Steady progress, especially in the fields of endocrinology and in biochemic investigations, has necessitated the inclusion of many new terms and names. However, a further increase in the bulk of the volume was prevented by the elimination of some of the older illustrations.

During preparation of this edition, Dr. Stedman died, at the age of eighty-four, and the work was finished by his nephew and former collaborator, Dr. Stanley Thomas Garber, who is now taking over the responsible task of editing future editions of this volume indispensable to the physician's library.

—*Hugo Ehrenfest.*

Two books[35, 36] by the same author may prove amazing examples of the formation of a new cult such as was based on the Abraham's apparatus a number of years ago, and which enjoyed a passing vogue. The author appears to be an extremely well-informed individual who follows the literature most minutely. His hypotheses and theories are too fantastic to deserve serious review. The entire subject matter is based upon an instrument called the Zykloskop which, in the first volume designed for the laity and called the Cycle of a Woman, Reform of Marriage, is designed to be a sort of a home guide. According to the author, by means of the reduction time determined by this modification of the spectroscope, ovulation can be readily determined and the so-called safe period thus definitely ascertained. By this same means, early pregnancy is supposed to be determined. It is a well-gotten-up monograph with excellent illustrations taken from standard sources (to whom no credit is given).

The second book is *Endogenous Endocrine Therapy in Gynecology*[36] in which a fantastic description of the cure of cancer, even with metastases, is said to have been obtained by means of stimulation of the pituitary with short wave radiation. This treatment is supposed to step up the function of the various endocrine glands and stimulate their activity, with resultant disappearance of the malignancies.

In the present disturbed world situation, I have no means of finding out what type of reception the theories of the author have been accorded in his own home, that is Holland. Doubtless in this country, cranks or charlatans will grasp at this type of diagnosis and treatment with avidity.

—*R. T. Frank.*

Scudder brings a recapitulation of his clinical and experimental research work on shock to the profession in this monograph *Shock: Blood Studies as a Guide to Therapy*.[37] After reviewing the nature of shock, discussing its similarity with certain phases of Asiatic cholera, and the evidence of his experiments and clinical research, he offers an evaluation of the various methods of treating shock which are in use today. He describes certain physical-chemical tests which, showing changes in hemoconcentration, are able to be used in a prognostic manner to bring earlier and more effective treatment in an early stage of shock. In the discussion regarding the changes in potassium in shock, he concludes that one of the variables

[33] **Die Krankhaften Psychischen Stoerungen der Rueckwandlungs-Jahre.** Von Professor Dr. Ferdinand Kehrer, Psychatrische und Nerven-Klinik, Universitaet in Muenster. Verlag von Julius Springer, Berlin, 1939.

[34] **Practical Medical Dictionary.** By Thomas Lathrop Stedman, M.D., and Stanley Thomas Garber, M.D. Fourteenth, revised edition, with etymologic and orthographic rules. Illustrated, 1303 pages. Williams & Wilkins Company, Baltimore, 1939.

[35] **Der Zyklus der Frau.** Reform des Ehelebens. Von Dr. Jules Samuels, Amsterdam. G. Naeff, The Hague, 1938.

[36] **Endogene Endokrinotherapie in der Gynaekologie.** Von Jules Samuels, Chirurg-Frauenarzt, Amsterdam. A. W. Sijthoff's Uitgeversmaatschappij, Leiden, Holland, 1938.

[37] **Shock: Blood Studies as a Guide to Therapy.** By John Scudder, M.D., Med. Sc. D., F.A.C.S. 235 pages and 55 illustrations, 5 plates. J. B. Lippincott Company, Philadelphia, Montreal, London, 1940.

produced by certain factors is an alteration in potassium metabolism, a derangement which serves as an indication of profound cell injury. He discusses the physical measures of hemoconcentration, and proceeds to evaluate them in experimental shock and shock due to other causes. He outlines the treatment employed in various types of shock and the results. He states finally that all factors which tend to maintain a normal ratio between the extracellular sodium and intracellular potassium are beneficial in the treatment of shock as they tend to favor normal action currents.

A laboratory manual is appended which discusses in detail the methods employed in studying hemoconcentration. There is a bibliography of some 500 references to the subject. This presentation should be of marked interest not only to the pathologist, but to the clinician in the treatment of shock.

—*Philip F. Williams.*

Dr. Robbins reviews the use of *Cyclopropane Anesthesia*[38] in this monograph. He discusses the physical and chemical properties of the agent, its effects upon the various systems and tissues, and proceeds with an exposition of the clinical administration of this gas. The complications and indications and contraindications are well set forth. Nor has he neglected to discuss the hazards in a chapter on explosions.

The book represents, too, a review of some 200 articles bearing on the subject, and the experiences which have been narrated in the use of the gas in some quarter million anesthesias. Particularly, and to the interest of the obstetrician, he brings out the relationship of the gas as an anesthetic in pregnancy to the elevated cardiac output. There is an excellent discussion of the relation of this anesthetic agent, and various types of sedation used in labor, to asphyxia of the newborn. The author feels that full surgical anesthesia with this agent can be produced in the mother without any interruption of fetal respiration.

It is particularly interesting to note his conclusions on page 129, in regard to anesthesia necessary in toxemia of pregnancy. He states that cyclopropane anesthesia produced no liver damage detectable by the bromosulphthalein test and that the kidneys show less disturbance after cyclopropane than after ether, and that the contractions of the gravid uterus are not altered by cyclopropane.

From a review of the literature one might conclude that preoperative medication is not necessary in operative obstetrics conducted with cyclopropane. It is mentioned that in a reported series of 400 cesarean sections under different agents, in 94 performed with cyclopropane there was less need for resuscitation measures and less evidence of postoperative gas pains. This book merits careful reading not only by the anesthetist but also by the clinician who must also judge what anesthetic his patient may need.

—*Philip F. Williams.*

Lewis and Hopper present a beautifully prepared monograph on *Medical Mycology.*[39] The material developed during a ten-year post-graduate course in dermatology, fortified by laboratory and clinical background. The illustrations are profuse and thoroughly correlative. The book is divided into two parts: The first dealing with the clinical, theoretic, and experimental aspects; and the second part concerning the laboratory methods. The first part presents a review of the various mycoses and fungus diseases in regard to diagnosis and treatment. The second part presents a detailed account of the technique of the various laboratory studies necessary in mycotic diseases. The book is thoroughly documented.

—*Philip F. Williams.*

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[38]**Cyclopropane Anesthesia.** By Benjamin H. Robbins, B.A., M.S., M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine. The Williams and Wilkins Company, Baltimore, 1940.

[39]**An Introduction to Medical Mycology.** By George M. Lewis, M.D., Associate, and Assistant Attending Dermatologist, New York Post-Graduate Medical School and Hospital, Columbia University, and Mary E. Hopper, M.S., Assistant in Mycology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. The Year Book Publishers, Inc., Chicago, Ill., 1939.

In this book, *Synopsis of Operative Surgery*,[40] Mobley gives a concise description of the technique of the more common surgical procedures. The fundamentals of anesthesia, postoperative care, and general considerations of surgical technique, hemorrhage, shock, drainage, and other pertinent topics are briefly, yet clearly, presented.

An excellent compendium for review, a well-illustrated guide for technique.

—*Philip F. Williams.*

This brochure, *Youth Looks at Cancer*,[41] is offered by the Westchester Cancer Committee of the American Society for the Control of Cancer, as a part of a general effort to educate the public in regard to this disease. The leaders of this Committee feel that through the use of the educational efforts depicted, such as field and laboratory work, motion picture films and technical exhibits, young people may be interested in the biologic aspects of the subject at an age when emphasis may be rendered without accompanying fright. To those who are interested in the campaign against cancer through education of the laity, this booklet should provide much valuable information.

—*Philip F. Williams.*

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[40]**Synopsis of Operative Surgery.** By H. E. Mobley, M.D., F.A.C.S. Chief of Surgery at St. Anthony's Hospital, Morrilton, Arkansas. 360 pages, 339 illustrations, 39 colored illustrations. The C. V. Mosby Company, St. Louis, Mo., 1940.

[41]**Youth Looks at Cancer.** The Westchester Cancer Committee. Brookville Press, Inc., Brookville, N. Y., 1940.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Endocrinology

Hamblen, E. C.: Clinical Correlates of Functional Uterine Bleeding, South M. J. **32:** 308, 1939.

While there is a tendency for the incidence of bleeding irregularities to "peak" during adolescence and the climacteric, an association of these with puerperal recovery and also with surgical and roentgenotherapeutic procedures results in a more even distribution of frequency among the different age groups. There is a strikingly low incidence among colored women. No general correlations exist between menarchal and menopausal ages and irregularities of bleeding. Parity apparently predisposes to their development. Fertility is lowered definitely by their existence.

The subjective symptomatology of patients with irregularities of flowing is varied: obesity and headache are common symptoms; dysmenorrhea is relatively infrequent. Gynecologic abnormalities and disease are encountered frequently in these patients.

In over 50 per cent there are one or more physical signs suggestive of endocrine disease. The greater portion of these signs is related to lowered function of the thyroid or of the ovaries. Little roentgenologic evidence of pituitary disease is encountered.

Most functional bleeding occurs from estrogenic endometriums, although any type of irregular bleeding may be associated with any of the normal or abnormal endometrial patterns. Excessively proliferated estrogenic endometriums occur most frequently in conjunction with climacteric menometrorrhagia. Various degrees of progestational proliferation are encountered commonly in the endometriums of patients having less severe irregularities. There are no irregularities which are peculiarly characteristic of the classical sex endocrine syndromes, except for that of hypo-ovarianism, in which amenorrhea and oligomenorrhea are common. Studies of the metabolism of progesterone in various types of irregularities by determinations of sodium pregnanediol glucuronide have indicated that the endometrial pattern from which bleeding occurs cannot be used reliably as an indicator of the functional level of the corpus luteum.

J. P. GREENHILL

Mocquot, P., and Palmer, R.: The Temperature Curve and Hormonal Actions in Gynecology, Presse méd. **48:** 305, 1940.

The authors maintain that the interrelating anatomic and physiologic phenomena which constitute the genital cycle can be interpreted, aside from menstruation, by some clinical manifestations apparent in the normal state, but capable of attaining more pronounced patterns in pathologic situations. Variation of the thermal curve is one of these manifestations. It shows a more or less regular periodicity, duration, constancy, and chronologic uniformity with various incidents and accidents during the genital cycle. These recorded thermal variations are important adjuncts to the diagnostic armamentarium of the hormonal status. Thermal variations make easier the diagnosis, classification, and treatment of certain pathologic conditions.

The writers advise that rectal temperatures be taken daily, at seven in the morning and five o'clock in the afternoon. The same clinical thermometer and the exact time of temperature taking are important as the variations of the thermal curve seldom exceed 2/10 to 4/10 of a degree. To establish the norm for each individual three months of temperature readings are adequate.

CLAIR E. FOLSOME

Turpin, Wm. R., Chassagne, P., and Lefebvre, J.: Prepubertal Megalothymia. A Planimetric Study of the Thymus During the Growth Period, Ann. d'endocrinol. **1:** 358, 1939.

The authors using the recently developed planigraphic technique studied the thymus gland in 82 children, 35 boys and 47 girls. The children's ages varied from 2 to 15 years.

The writers state that the planigraphs obtained in the study demonstrate an increasing volume of the thymus during the growth period of the child. The maximal volume is reached at the time of puberty and warrants terming the clinical entity, as "prepubertal megalothymia." The maximal increase occurs later in boys than in girls and this difference is particularly striking in opposite sexed twins.

The prepubertal megalothymic shadows disappear one or two years following puberty.

The authors describe this new technique in excellent detail and the article is well illustrated with graphs, charts, and 10 photographs.

CLAIR E. FOLSOME

Westman, Axel: Differential Diagnostic Problem in Virilizing Diseases of Women, Acta obst. et gynec. Scandinav. **19:** 455, 1939.

Westman reports three cases of pronounced symptoms of virilism. The first case was a marked Cushing type with very round face and considerable obesity of the breast and abdomen, while the extremities were thin. The patient also showed a strong growth of beard, numerous striae formations, increased blood pressure, and signs of marked osteoporosis. The ovaries were atrophic, and the patient was suffering from amenorrhea. X-ray treatment of the pituitary body led to a partial improvement.

The second case resembled the first, but striae formations and osteoporosis were not present. A large suprarenal adenoma was found on the right side and was extirpated. The third case presented a virile hirsute type. The patient had a deep bass voice. She suffered from amenorrhea, and a marked hypertrophy of the clitoris was present. The distribution of fat, on the other hand, was normal. No increase of blood pressure was present, nor changes in the skin. One of the ovaries was the seat of an arrhenoblastoma and one suprarenal was markedly enlarged. After the ovarian tumor had been removed, the growth of hair decreased, particularly in the face, and the menstruation became normal. The change in the voice remained, however, as did also the hypertrophy of the clitoris, and it is debatable whether this should not be considered to be due to an excessive functioning on the part of the enlarged suprarenal gland.

The cases illustrate the diagnostic difficulties in discovering the cause of virilism in women. Similar pictures of symptoms may be caused by tumor formations either of the pituitary body, the suprarenal glands, or the ovaries.

J. P. GREENHILL

Stabler, Frank, and Thomson, J. Greig: Granulosa-Cell Tumour with Precocious Sexual Development in a Child Aged Six, J. Obst. & Gynaec. Brit. Emp. **47:** 199, 1940.

The authors report a case of a child aged six years and two months who developed signs of sexual precocity, followed by marked vaginal bleeding. Examination revealed an abdominal tumor which on laparotomy proved to be a left-sided ovarian cyst. On microscopic examination it was found to be a granulosa-cell

tumor. Blood studies showed only a moderate increase in the amount of circulating estrin. The endometrium was that of a sexually mature adult, with prominent, dilated endometrial glands. An interesting feature of the chemical analysis of this tumor was that 40 per cent of the tumor was composed of lipoids. The authors feel that tumors associated with marked clinical signs of hormone production contain large quantities of lipoids. After removal of the tumor there was incomplete retrogression of the secondary sexual characteristics.

WILLIAM BERMAN

Baruk, David, Racine, and Mlle. Leuret: Folliculin Psychoses and Circulatory Disturbances (Experimental Study on the Action of Folliculin upon the Cerebral Circulation), Presse méd. **48**: 281, 1940.

The authors review the role of hyperfolliculinism upon the psyche and discuss the varying degrees of mental changes occurring from the minor vasomotor manifestations to the more marked major psychoses.

Experimentally they exposed the cerebrums of rabbits and monkeys to direct observation by a method described by both Riser and Villaret and others. Both oily and water solutions of folliculin were used and both types produced the same response, although the response to the aqueous solution was more rapid.

They found that folliculin injection into the animals produces a distinct diffuse vasodilatation of the cerebral circulation effective upon both large and small vessels. The brain appears congested while the vessels seem turgid. Biopsy specimens of the brains reveal distinct increase in vascularity as opposed to specimens from control animals.

CLAIR E. FOLSOME

Maranon, Richet, Pergola and Lesueur: Secondary Tetany from Hyperfolliculinemia, Ann. d'endocrinol. **1**: 142, 1939.

The authors are of the opinion that other endocrine influences, distinct from the parathyroid, can also be pathogenic in the development of the tetany syndrome. They cite 4 cases of tetany induced by excessive folliculin, two of them being males. Both of these males had a folliculinemia.

Case 2 was a young man of 20 years who had been operated upon at the age of 18 for the reduction of a bilateral cryptorchidism. There were found 800 I.U. of folliculin per 1000 c.c. of urine. He developed a latent tetany with paroxysmal crises. Marked relief followed testosterone propionate treatment.

Case 3 was a male of 49 years who had chronic and paroxysmal tetany. It was determined that there were 150 to 300 I.U. of folliculin per 1 liter in the urine. Testosterone treatment caused the tetany to disappear.

Both female patients presented a tetany. In Case 1 the patient experienced a severe and typical tetany crisis when folliculin was accidentally given intravenously. The patient in Case 4 secured marked relief from premenstrual tetany with the combined treatment of luteal and testicular hormones.

The authors believe the hypothesis best explaining this correlation is that excessive folliculin may directly modify the calcium metabolism by reducing parathyroid secretion.

CLAIR E. FOLSOME

Ramos, Alberto Peralta: The Quantitative Analysis of Folliculin as the Basis of Clinical and Therapeutic Orientation in Gynecology, Presse méd. **48**: 270, 1940.

The author summarizes the known physiologic facts of folliculin and its interrelationships with other hormones. He believes that blood and urinary folliculin levels must be known to treat correctly the functional hemorrhages, and in particular those occurring in puberty and menopause.

Six elaborate charts are presented in the paper. In Charts 2 and 3 it is noted where the author indicates that folliculin is released to act directly upon the "sexual center of the diencephalon."

Ramos concludes that estrogen therapy should be used conservatively; that the correlation of the clinical symptomatology with the curves of folliculin constitute the most important fundamental for diagnosis and treatment in gynecic endocrine dysfunction.

CLAIR E. FOLSOME

Chiray, M., Mollard, H., and Duret, M.: Asthma and Disturbances of the Ovarian Endocrine Secretions, Presse méd. **48**: 201, 1940.

Clinical evidence that there exists a relationship of altered ovarian activity to certain asthmatic cases can be placed in three categories: In one group the periods of the patients are normal and they note increased asthmatic attacks occurring in the premenstrual period; in a second group the asthma appears during manifest menstrual disorders and has an apparent predilection during amenorrheic episodes; last, there are those late cases of asthma which first occur with the onset of the menopause. Because of these facts one can describe those cases of asthma which are coexistent with rhythmic cycles or associated with menstrual disturbances, as ovarian asthmas.

The authors discuss 3 cases of ovarian asthma. In each the asthma was exacerbated during the inter- or premenstrual period. All 3 patients obtained excellent relief from repeated testosterone injections (10 mg.) in the premenstrual period and the writers conclude that in these cases the ovarian asthma was due to hyperfolliculinemia.

CLAIR E. FOLSOME

Heller, C. G., and Heller, Emily F.: Gonadotropic Hormone; Urine Assays of Normally Cycling, Menopausal, Castrated, and Estrin Treated Human Females, J. Clin. Investigation **18**: 171, 1939.

Urines from 66 menopausal women were assayed by them for gonadotropic potency. It was found that their potency was not related to the presence or absence of symptoms, age, hysterectomy, or the involution. No difference in gonadotropic potency was found between menopausal women with symptoms and senile women, castrated women or menopausal women without symptoms. Urinary gonadotropic concentration was low in women with regular normal menstrual cycles, high in menopausal women in whom cycles had ceased, and intermediate in menopausal women with irregular cycles. Estrogen treatment alleviated the vasomotor symptoms of 15 menopausal women but failed to reduce concurrently their gonadotropic potency. Continued estrogen therapy caused a slight reduction in potency, but failed to suppress it by significant amounts.

J. P. GREENHILL

Bagby, B. B.: Urinary Prolan Excretion during a Menstrual Cycle, J. Lab. & Clin. Med. **25**: 687, 1940.

The urinary prolan excretion of a normal woman was determined daily for one month, on the first morning specimen, using ovarian and uterine weights of immature rats as indicators. Prolan was found on the fifteenth and sixteenth days prior to the next menses.

HUGO EHRENFEST

Contamin, R., and Leraillez, F.: The Clinical Use and Therapeutic Results from Gonadotrophic Hormone, Presse méd. **47**: 1660, 1939.

Sixty women with gynecologic disorders were treated with gonadotrophic hormone. Gonadotropes of both serum and urinary origin were used. The treatment was uniform in that 5 to 6 intramuscular injections, one every forty-eight hours, were given, starting the second day after the end of the period and repeated each month for three months.

Six of seven patients with secondary amenorrhea had resumption of normal menses. Five of 8 cases of juvenile primary dysmenorrhea were made better and

the psychic difficulty of this group was unusually improved. In all three cases of pubertal hemorrhages the results were excellent. In the 26 cases of adult women with dysmenorrhea only those with concomitant menorrhagias obtained the most direct results. No figures are given relative to this group. In 11 cases of sterility, on the basis of endocrine imbalance, 8 had primary sterility and but 1 became pregnant, while one of the 3 secondary sterility patients became pregnant.

In all 7 instances menopausal bleeding was easily controlled by gonadotropic hormone although 2 of these patients underwent subsequent laparotomy. The authors also treated 1 patient with eczema of the face and hands associated with hypoestrination; 2 patients with habitual abortion; 3 patients with pruritus vulvae and 2 with menorrhagia on the basis of cystic ovaries. All of this latter group obtained partial or complete relief from their complaints.

The writers conclude that gonadotrophic hormone is an efficacious aid in the treatment of the female functional disorders.

CLAIR E. FOLSOME

Fluhmann, Frederic: Biologic Characteristics of Equine Gonadotropic Hormone, West. J. Surg. Obst. & Gynec. **48:** 63, 1940.

The equine gonadotropic hormone was discovered in 1930 by Cole and Hart. It occurs in high concentration in the blood of pregnant mares but is present only in slight traces in the urine. The biologic characteristics of this hormone show many properties common to the other known gonadotropes, but it appears to be an entirely new entity. It probably is not a product of the hypophysis but another "pregnancy hormone."

The exact effect of this equine hormone on the human ovary is not definitely known. Davis and Koff claimed to have produced ovulation in 16 out of 36 women. But such effectiveness is doubted by others, by Hartman on the basis of extensive experiments on monkeys. Clinically, the hormone has been employed in the treatment of amenorrhea, sterility, metropathia hemorrhagica, etc. Some of the reported results are surprising, thus as Hall's who found that 24 out of 43 sterile women became pregnant following this treatment.

The author's clinical experience in 15 patients so far has not been at all encouraging. Further extensive observations will be required to determine the correct selection of cases, proper dosage, and most favorable time of administration.

HUGO EHRENFEST

Varangot, J.: Endocrine Therapy of the Dysmenorrheas, Presse méd. **48:** 220, 1940.

The author used hormonal therapy in treating 27 cases of dysmenorrhea. Twenty of these patients were followed a sufficient time to permit conclusions. Nine of this latter group had primary dysmenorrhea.

Massive folliculin therapy gives satisfactory results in cases of dysmenorrhea due to uterine hypoplasia. The author has not had sufficient experience with testosterone to warrant an opinion of its efficacy. Last, progesterone gives excellent results in primary dysmenorrhea, if used in sufficiently large doses (20 to 25 mg. progesterone, 4 to 5 times, in the week preceding the period).

CLAIR E. FOLSOME

Dick, M., and Hooker, C. W.: Absence of Acute Effects of Sex Hormones, J. Lab. & Clin. Med. **25:** 33, 1939.

Six young adult dogs were studied under morphine-sodium barbital anesthesia. After intravenous injection of sex hormones, heart rate, blood pressure, and respiration were recorded and followed for periods up to six hours in both intact and castrate animals. No significant alterations were noted following injection of 50 mg. of testosterone propionate, 50,000 I. U. estradiol benzoate, or 400 I. U. of theelin.

R. J. WEISSMAN

Deanesly, Ruth: Depression of Hypophyseal Activity by the Implantation of Tablets of Oestrone and Oestradiol, J. Endocrinol. (London) **1**: 36, 1939.

The author implanted estrone tablets, 2.25 to 16 mg.; and estradiol tablets, 11.8 to 16.5 mg., under the skin of normal male mice and rats of varying weights and permitted the tablets to remain subcutaneously for 10 to 270 days.

This treatment, like continued injections of estrogens, causes inhibition of some of the functions of the pituitary gland. It leads to marked depression of the growth rate, loss of fertility, shrinkage of gonads and accessory organs, and enlargement of the adrenals and pituitary gland. These changes, studied in detail during recovery period, were reversible after removal of the estrone or estradiol tablets.

Three rats with estradiol tablets implanted for 270 days developed tumors of the pituitary gland, which would probably eventually have proved fatal.

The author includes records showing the rate of absorption of the tablets.

CLAIR E. FOLSOME

Herrnberger, K.: The Influence of Estrin on the Vaginal Epithelium of Young Girls, Arch. f. Gynäk. **167**: 506, 1938.

The author used estradiol benzoate in the treatment of gonorrheal vulvovaginitis in a group of 82 girls ranging in age from 6 months to 12 years. This form of hormone therapy is most efficacious, depending upon the stimulation and production of a mature vaginal mucosa. This maturation can be brought about in approximately 17 days, following a single intramuscular injection of 10,000 units of estradiol benzoate and follows such an injection in every instance. The optimum dosage, that is the least amount of hormone necessary for the maintenance of such epithelial maturation without the production of pathologic changes in the uterus and ovaries, was found to be 1,000 units of the alcoholic solution of estradiol benzoate given daily. Such daily minimal doses have no effect upon ovary or pituitary in the vast majority of instances. In the very occasional patient in whom pituitary or ovarian changes are produced no harm is done, first because such reactions are reversible and second because they tend to disappear when the medication is stopped.

RALPH A. REIS

Sharpey-Schafer, E. P., and Schrire, I.: Effect of Oestrogens on the Urinary Volume, Lancet **2**: 973, 1939.

In a group of 14 hospitalized patients, on a controlled diet, the daily injection of 100,000 I. B. U. of estradiol benzoate for ten days did not result in a change in urinary output. The group of patients included 3 men, 3 normal menstruating, 6 postmenopausal women, and two castrate women.

CARL P. HUBER

Moricard, R., and Simard, R.: Comparative Study on the Activity of Oestradiol Benzoate, Vitamins A and C, and Diethylstilboesterol in Experimental Fibromatosis, Ann. d'endocrinol. **1**: 399, 1939-1940.

The authors demonstrate that it is possible to produce fibromas in the female guinea pig by continuous intraperitoneal injections of estradiol benzoate, 1.0 mg. per week for four months. The fibromas can also be produced by intermittent treatment, provided the total dose of estradiol treatment remains the same.

Vitamin A (3 mg., 5000 I. U., per week intraperitoneally), when added to the estradiol benzoate did not appear to modify the production of fibrous neoplasms, uterine or abdominal, while the addition of vitamin C (100 mg., 2,000 I. U., per week intraperitoneally) to the estradiol benzoate accentuated the formation of new growths.

The injection of diethylstilbestrol, 0.25 mg. per week, for several months, produced a uterine fibrosis much less important than that inducted by the 1 mg. per week dose of estradiol benzoate. Diethylstilbestrol caused marked cystic hyperplasia of the uterine mucosa.

CLAIR E. FOLSOME

Weed, J. C., and Collins, C. G.: The Treatment of Infant Vulvovaginitis with Estrogenic Hormone, South. M. J. 32: 1000, 1939.

The introduction of estrogenic hormone simplified treatment of infantile vulvovaginitis and improved results. Of the three methods of administration, the oral requires at least four times the dose of the hypodermic. Vaginal suppositories have in their favor: (1) Ease of administration, an important factor in children; (2) efficient, direct action; and (3) the possibility of home treatment. Furthermore, such undesirable side effects as breast enlargement and congestion of the vulva that accompany hypodermic administration of the estrogens were not observed in this series treated by suppositories.

Estrogenic hormone causes an increase in the thickness of the stratified squamous epithelium from the six to eight cell layers of the infant vaginal mucosa to the fifteen to twenty cell layers of the adult structure, with cornification, increase of glycogen desposits, and lowered surface pH. In gonococcal vulvovaginitis histologic changes in the mucosa are accompanied by an alteration in the character of the discharge: from an excoriating, greenish one to a thick, creamy exudate containing many saprophytic gram-negative organisms with gram-positive rods, and few or no pus cells.

This report is based upon 23 cured cases of gonococcal vulvovaginitis with adequate follow-up. It is recommended as a preliminary measure to treatment that all patients be examined rectally in order to rule out the possibility of foreign body. Cleansing of the vulva with soap and warm water by the mother twice a day was employed by the gynecologic and pediatric services. The urologic service in addition used vaginal irrigations of weak potassium permanganate at each office visit. This procedure was not thought to have any particular value.

Actual treatment consisted in the nightly insertion of vaginal suppositories containing 1,000 international units of estrogenic hormone for 18 to 24 doses. Experience showed that 18,000 units was a minimal dose. The results of weekly vaginal smears served to indicate whether additional therapy was necessary. For release, four negative smears were required and follow-up examinations were made one and two months later. Of the series, there were 6 recurrences which required additional therapy. One resistant case was found to have a urethritis, and supplementary sulfanilamide therapy was given. A small hymenal opening prevented insertion of the suppository in a few cases, and it was necessary to pass a Kelly endoscope.

ARNOLD GOLDBERGER

Huet, J. A., Comte, R. J., and Hershberg, A. D.: Diethylstilbestrol, the Synthetic Estrogenic Substance, Gynecologia 38: 517, 1939.

The authors used stilbestrol in 46 cases and found the drug to be useful in cases of infantilism of the sex organs, in certain cases of oligomenorrhea and dysmenorrhea, in functional disturbances of the menopause and in some instances of hypophyseal-ovarian dysequilibrium. In the cases of menstrual disturbances success was observed in 77 per cent, and in the menopausal cases the incidence of relief was 82 per cent. Disagreeable symptoms such as nausea and asthenia occurred in 10 per cent of the cases, but they were serious in only 3 per cent.

The authors are enthusiastic about stilbestrol, because it is effective by mouth and it is cheap. However, as with all medication, an accurate diagnosis must be made before it is prescribed.

J. P. GREENHILL

Felding, S., and Møller-Christensen, E.: Clinical Experience with Diethylstilboestrol, Acta obst. et gynec. Scandinav. **19:** 337, 1939.

After a short account of the biologic characteristics of Diethylstilbestrol, the writers report results obtained with the substance in 45 patients with ovarian deficiency symptoms and 10 patients with hypoplasia of the uterus. They conclude that the drug has proved to be on a par with estrone preparations. In about one-sixth of the patients, it caused nausea and vomiting, in some cases to such a degree that the treatment had to be suspended.

J. P. GREENHILL

Wenner, Robert, and Joel, Karl: Stilboestrol and Anhydro-Oxyprogesterone, Lancet **2:** 688, 1939.

The effect of stilbestrol and anhydro-oxy-progesterone on a patient who was thirteen years postmenopausal and on 8 women castrated by x-ray therapy was studied; 25 mg. of stilbestrol by mouth or 15 mg. by intramuscular injection were required to produce proliferation of a resting or atrophic endometrium. Cystic glandular hyperplasia could be produced by 50 to 60 mg. given by mouth. The administration of 220 to 300 mg. of anhydro-oxy-progesterone produced progestational changes in the proliferated endometrium and resulted in the occurrence of a menstruation. In two of the patients fatigue, general weakness, and nausea, with vomiting in one case, appeared as side effects after stilbestrol administration. No secondary symptoms appeared after the administration of anhydro-oxy-progesterone in doses as high as 25 mg. Lactation was either prevented or inhibited in 20 women by 5 to 15 mg. of stilbestrol by mouth. In six of these cases administration of 5 to 10 mg. in a single dose during the twenty-four hours after delivery prevented the onset of lactation. In 14 cases stilbestrol was given to inhibit established lactation with satisfactory results in all but two cases. Smaller doses were effective in preventing lactation than in inhibiting established milk secretion. Doses greater than 20 mg. were not given.

CARL P. HUBER

Lorenzetti, Filiberto: Observations on the Therapeutic Properties of Diethylstilbestrol, Gynecologia **6:** 89, 1940.

The writer has used the drug in a small series of 20 cases.

One patient was relieved of pruritus vulvae following biweekly injections of 0.5 mg. with a total dosage of 4.20 mg. Four patients having menopausal symptoms all reported relief although one patient experienced gastric disturbance with its use. Two patients with oligo- and hypomenorrhea with associated primary dysmenorrhea obtained relief from stilbestrol.

Stilbestrol used during the first six days of the puerperium in 7 cases after premature delivery of stillborn fetuses prevented lactation.

In 5 cases of surgical menopause the drug relieved vasomotor symptoms, but one patient in this group experienced nausea.

The author concludes that stilbestrol is a valuable addition to gynecologic therapy and particularly in patients presenting subestrogenic levels and in those requiring substitutional treatment during the menopause.

CLAIR E. FOLSOME

Bishop, P. M. F., et al.: Oestrogenic Properties of Stilbestrol Dipropionate and Hexoestrol, Lancet **1:** 629, 1940.

Stilbestrol dipropionate and hexestrol have estrogenic properties similar to those of stilbestrol so far as they are capable of: (1) Inducing uterine hemorrhage in cases of amenorrhea; (2) relieving the symptoms of the menopausal syndrome; (3) leading to the appearance of cornified cells in the vaginal smear in menopausal

cases; (4) restoring the normal condition of the vulva and vagina in senile atrophic vaginitis; (5) relieving the pain of dysmenorrhea; and (6) inhibiting lactation.

Toxic effects (particularly nausea and vomiting), although not severe, developed in 21.6 per cent of patients treated with stilbestrol dipropionate and 4.5 per cent of cases treated with hexestrol. Toxic symptoms are more likely to develop when large doses are given. They also tend to disappear if treatment is persisted in.

CARL P. HUBER

Lipschutz, Alexander, and Vargas, Luis Jr.: Tumorigenic Powers of Stilboestrol and Follicular Hormones, Lancet **1**: 541, 1940.

The authors corroborate their previous report that stilbestrol has a much greater tumorigenic effect than the natural estrogenic substances (estradiol and estrone). In the guinea pig, 100 to 200 mg. of estradiol per injection is necessary to produce a reaction comparable to 3 to 10 mg. of stilbestrol per injection. As much as 3 to 10 mg. of stilbestrol given three times weekly for about three months is necessary to develop uterine and extrauterine fibroids in the guinea pig. The tumorigenic action of small doses of stilbestrol is, however, less than that of similar doses of esterified estradiol (monobenzoate and dipropionate). The guinea pig uterus increases beyond the normal weight more rapidly with stilbestrol than with the free natural estrogens. This is tentatively explained by an inability of the organism to inactivate stilbestrol as rapidly and effectively. Uterine bleeding in the guinea pig is more frequent with stilbestrol than with the natural estrogens, but not more commonly encountered than with similar quantities of the esterified hormones.

CARL P. HUBER

McLellan, Archibald: Response of Non-Gravid Human Uterus to Posterior-Pituitary Extract and Its Fractions Oxytocin and Vasopressin, Lancet **1**: 919, 1940.

Sixty records were obtained from 43 normal nongravid women during various stages of the menstrual cycle. All were in the reproductive age group and 34 had borne children. Uterine contractions were recorded following the insertion of a small bag. The uterus was found to respond to posterior pituitary extract immediately before and during menstruation and in the early interval phase of the cycle. Contractions of the nongravid uterus are produced by vasopressin but not at all by oxytocin.

CARL P. HUBER

Hohlweg: The Corpus Luteum Hormone Effect of Desoxycorticosteron, Zentralbl. f. Gynäk. **63**: 1143, 1939.

The writer found that desoxycorticosterone produces a corpus luteum hormone effect in infantile rabbits prepared with estrin. However, this substance has only one-tenth the effect of progesterone and not one-half as claimed by Hoffmann. In castrate infantile rabbits, positive uterine reactions could not be obtained even with 80 mg. of desoxycorticosterone. The author could not produce a secretory endometrium in a single case even with much larger doses than were used by Hoffmann.

J. P. GREENHILL

Vautrin, Guillermo: Hormonal Treatment of Uterine Hyperkinesia with the Corpus Luteum Hormone, Rev. méd. cubana **51**: 1, 1940.

Vautrin used the hormone of the corpus luteum as a sedative for uterine contractions in certain muscular kinesias or hypertonic conditions of the uterus in labor. He believes that successful dosage is neither in "drops nor in pitcherfuls," but in the proper amounts. It fluctuates between 10 and 20 mg. The route of introduction used was the intramuscular one. A belladonna derivative must be used in conjunction with the progesterone, if hyperkinesia is accompanied by cervical spasm.

As the author points out, progesterone is the antagonist of the follicle hormone and therefore, from the hormonal aspect, is the specific in cases in which the uterus reacts violently to the action of the follicular-pituitrin interrelation.

The use of the corpus luteum hormone has an advantage over morphine, because it is not toxic for the fetus. The sedative action of progesterone makes it the medicament par excellence when used in childbirth for excessively strong uterine contractions. If the inhibiting therapeutic action of progesterone produces uterine inactivity not desirable during labor, it is advisable to use pitocin (oxytocin) intravenously, especially in cases of hemorrhage.

J. P. GREENHILL

Warwick, M. H., and Parkes, A. S.: Absorption of Progesterone and Desoxycorticosterone (From Tablets Implanted Subcutaneously), Lancet **1:** 406, 1940.

Experimental studies with the subcutaneous implantation of progesterone in the human being, goat, guinea pig, and rat reveal that from large tablets the average rate of absorption is about 20 per cent per month. Tablets weighing 50 mg. thus supply about 10 mg. per month.

Similar studies with desoxycorticosterone implanted subcutaneously in rats revealed that the rate of absorption is about twice that of desoxycorticosterone acetate. Implantation of 70 mg. tablets of the free material supplies a minimum of 4 mg. daily for one month. The use of free desoxycorticosterone is therefore suggested when heavy dosage is required.

CARL P. HUBER

Falls, Frederick H.: The Use of Progestin in Obstetrical Complications, Illinois M. J. **77:** 180, 1940.

The author presents both clinical and laboratory evidence to prove that the use of progestin in obstetric complications, such as threatened abortion, premature separation of the placenta, and premature rupture of the membranes, is of great value, for this hormone is antagonistic toward uterine contractibility and uterine irritability. In several cases where the membranes ruptured prematurely, Falls was successful in preventing the onset of uterine contractions for varying periods of time, from a few days up to a month. In 17 cases of threatened and habitual abortion, 14 patients were successfully treated with progestin. During the past year he has treated successfully 9 partial detachments of the placenta, 10 premature labors, 1 premature rupture of the membranes, 1 placenta previa, and 2 habitual abortions, whereas treatment was unsuccessful in 1 habitual abortion, 1 threatened abortion, 2 premature ruptures of the membranes, and 1 premature separation of the placenta.

EUGENE S. AUER

Beilly, Jacob S., and Solomon, Samuel: The Inhibition of Lactation Post-Partum with Testosterone Propionate, Endocrinology **26:** 236, 1940.

In a group of 108 patients, the inhibition of lactation, post partum, by means of testosterone propionate was studied. Complete inhibition occurred in 58 per cent, incomplete results in 40 per cent. All the patients obtained relief from engorgement or distention and pain or discomfort in the breasts. Failure occurred in 2 per cent.

J. THORNWELL WITHERSPOON

Vermelin, H.: Happy Results with Progesterone in Troubles of Nidation, Bull. Soc. d'obst. et de gynéc. **28:** 540, 1940.

The author succeeded in preventing miscarriage in two cases of threatened abortion by means of progesterone. Pains and bleeding stopped rapidly after the drug was given.

The author favors the prophylactic rather than the curative use of progesterone and prefers small doses frequently repeated to a few large doses. In his two cases he had difficulty in delivering the placenta. He attributes this to excessive growth of villi at the time of nidation, as the result of the progesterone.

J. P. GREENHILL

Rubinstein, H. S.: The Rationale of the Use of Testosterone Propionate in Functional Uterine Bleeding and Dysmenorrhea, J. Lab. & Clin. Med. **24**: 1026, 1939.

Testosterone propionate in adequate dosage will relieve functional uterine bleeding and dysmenorrhea.

Ovulation is suppressed by repeated injections and the chemical similarity between this substance and progesterone may explain its progesterone-like effect. The amenorrhea following injection of large doses of testosterone propionate is probably due to the inhibition of the pituitary gland with a suppression in output of pituitary gonadotropic substance. With the diminution of estrogenic concentration, uterine relaxation is produced and this checks the continuation of the interval endometrium, and this in turn checks bleeding and pain.

W. B. SERBIN

Pierra, L. M., and Erlande, G.: The Place of the Male Hormone in Gynecology, Rev. franç de gynéc. et d'obst. **35**: 97, 1940.

The authors have used the male hormone in four types of female disturbances: congestive disturbances associated with ovulation, chronic mastitis, simple premenstrual congestion of the breasts, and fibroids of the uterus.

In a series of 12 women with ovulation pain only two were definitely relieved by testosterone propionate. On the other hand, 11 of 14 women with simple premenstrual mammary congestion were helped by testosterone. In cases of fibroids of the uterus, the male hormone produced cessation of excessive bleeding in the 7 cases in which it was used. However, in only 3 cases was there an apparent diminution in the size of the neoplasms.

J. P. GREENHILL

Kenny, Meave, and King, Earl: Effect of Prolactin on Lactation in Nursing Women, Lancet **2**: 828, 1939.

Two preparations of prolactin, one from ox pituitary and the other from sheep, were administered to 43 women deficient in milk secretion, selected at times during the period of lactation varying from the immediate puerperium to eight weeks after delivery. The dosage consisted of 300 Riddle units on the first and second days of treatment, 120 units on the third and fourth days, 60 units on the fifth day of treatment. No local or systemic ill effects were noted. The response in increased milk secretion was encouraging. An increase of over three ounces of milk per day was considered a positive response. A positive response occurred in 74 per cent of the prolactin treated group, and in 21 per cent of a control group treated by nonendocrine methods. Depression of the gonadotropic function was not observed. The quality of milk secreted after the administration of the extracts was essentially the same as that of the control samples.

CARL P. HUBER

Kaijser, Kurt G.: The Effect of Prolactin on the Secretion of Milk in Women in the Puerperium and for the First Few Months After Parturition as Well as in Newborn Babies, Acta med. Scandinav. **104**: Suppl. I-II, 1940.

Kaijser tested the lactation-stimulating and lactation-maintaining action of prolactin, administered intramuscularly, in newly delivered women, nursing mothers in whom hypogalactia later appeared and babies up to a few months old. Prolactin

is a hypothetical hormone of the anterior lobe of the hypophysis, which is not prepared in a chemically pure form, but is obtained in an extract from the pituitary body.

With regard to the ability of prolactin to act as a stimulus to lactation, the author's results do not definitely prove this with the dosage and the product used. However, increase in the secretion of milk was seemingly obtained in the cases in which the injections of prolactin were given relatively soon after parturition.

The author believes he has introduced a new method in the field of experimentation with prolactin, in that he studied its effect on the production of witch's milk in infants during the first few months of life. In a number of cases he succeeded in demonstrating a slight increase in the glandular tissue of the infants and in a few cases the appearance of milky fluid in very small quantities upon mild pressure on the breasts.

Finally, mention is made of the possibility of a quantitative and qualitative daily rhythm in milk secretion.

Not until the existence of such a rhythm is established and thoroughly understood will it be possible to test with any degree of certainty the action on nursing women of a hormone necessary for the institution and maintenance of lactation.

J. P. GREENHILL

Item

American Board of Obstetrics and Gynecology

In accordance with its Articles of Incorporation, the American Board of Obstetrics and Gynecology has elected Dr. Norman F. Miller of Ann Arbor, Michigan, and Dr. Willard R. Cooke of Galveston, Texas, as members, directors, and examiners, to fill the unexpired terms of Dr. Jennings C. Litzenberg and Dr. Grandison D. Royston, both of whom resigned on October 15, 1940. These replacements make a total of four changes in personnel on the Board during the past three years.

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held in June, 1941.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, from May 28 to June 1, 1941, immediately prior to the opening of the annual meeting of the American Medical Association.

Application for admission to Group A (Part II) examinations must be on file in the Secretary's Office not later than March 15, 1941.

After March 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

The Board wishes to announce a modification of the case record ruling (effective January 1, 1942) as it appears in the September, 1940, issue of the Board booklet. This ruling should read: "It is preferable that the number of residency cases submitted should not be more than half (25) of the total number of fifty (50) cases required."

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Books Received

GETTING READY TO BE A MOTHER. By Carolyn Conant Van Blarcom. Revised by Hazel Corbin, general director of Maternity Center Association. Fourth edition, 190 pages, illustrated. The Macmillan Company, New York, 1940.

CHILD CARE AND TRAINING. By Marion L. Faegre, assistant professor of parent education, and John E. Anderson, director of Institute of Child Welfare, University of Minnesota. Fifth edition, revised, 320 pages, illustrated. The University of Minnesota Press, Minneapolis, 1940.

REPORT ON THE SEX QUESTION by the Swedish Population Commission. Translated and edited by Virginia Clay Hamilton, M.D. Published for the National Committee on Maternal Health, Inc. Williams & Wilkins Company, Baltimore, 1940.

PHYSIOLOGY OF MICTURITION. By Orthello R. Langworthy, Lawrence C. Kolb and Lloyd G. Lewis, sub-department of neurology and James Buchanan Brady Urological Institute of Johns Hopkins University. 232 pages, illustrated. Williams & Wilkins Company, Baltimore, 1940.

GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY, with clinical and endocrine relations. By Emil Novak, associate in gynecology, Johns Hopkins Medical School, etc. 496 pages with 427 illustrations. W. B. Saunders Company, Philadelphia, 1940.

MODERN MARRIAGE. By Paul Popenoe, general director, American Institute of Family Relations, Los Angeles, Calif., etc. Second edition, 299 pages. The Macmillan Co., New York, 1940.

OBSTETRICS IN GENERAL PRACTICE. By J. P. Greenhill, M.D., professor of obstetrics and gynecology, Loyola University Medical School, Chicago, etc. 448 pages, 112 illustrations. Year Book Publishers, Inc., Chicago, 1940.

CONTROLLED FERTILITY. An evaluation of clinic service. By Regine K. Stix, M.D., research associate, Milbank Memorial Fund, and Frank W. Notestein, Ph.D., lecturer in School of Public Affairs, Princeton University. The Williams & Wilkins Company, Baltimore, 1940.

ETUDOS CIRURGICOS. By Eurico Branco Ribeiro, director do Sanatorio São Lucas. 219 pages, illustrated. Sociedade Editora Medica Limitada, São Paulo, Brasil. 1940.

LA MANIOBRA ANO PARIETO-ABDOMINAL EN LOS PROCESOS AGGUDOS DEL ABDOMEN. Por Dr. Emilio S. Sammartino. El Ateneo, liberia y editorial. Buenos Aires, 1940.

ATTAINING WOMANHOOD. By George W. Corner, M.D., professor of anatomy, University of Rochester School of Medicine. 95 pages, illustrated. Harper & Brothers, New York, 1940.

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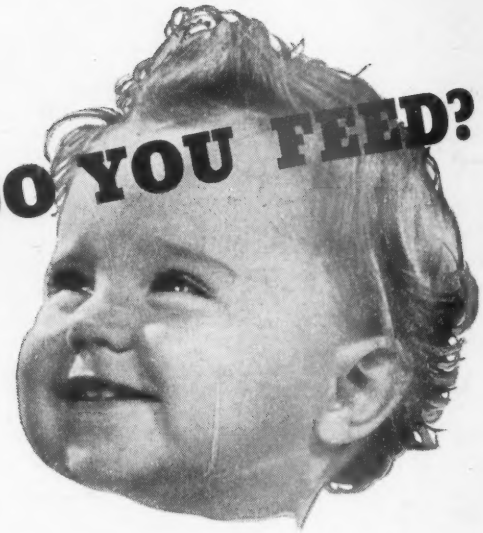

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